GEI-067

#21

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application: Lanquetin et al.
Serial No 09/284,147 Art Unit: 1616
Filed on: April 7, 1999 Examiner: Qazi

for: New contraceptive medicinal product and method for its preparation

DECLARATION UNDER 37 C.F.R. § 1.132

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

The undersigned, Jean-Louis THOMAS, of France, declares as follows:

I am a Medical Doctor (MD) and a Pharmacist holding such degree from the University of Nancy (France).

I have fulfilled the following functions:

1969-1972: Pharmacist Resident, Nancy hospitals

1973-1975: Consulting Pharmacist, Nancy hospitals

1975-1976: Medical Resident, Hôpital des Armées, Nancy

1976-1980: Medical Resident, Nancy hospitals

1980-1984: Assistant Resident, Centre Hospitalier Universitaire (CHU),Nancy

1984-1985: Senior Consultant-Assistant professor, CHU Nancy

1985-1987: Senior Consultant, Nancy hospitals

Since 1985: Director of the clinical Research and Development Department, Théramex Laboratory, Paris

Since 1988: Senior Consultant, Paris hospitals (Department of Endocrinology, Diabetology and Nutrition, CHU Henri-Mondor, Créteil)

I devoted many years of my professional life in the field of Endocrinology and Clinical Pharmacology.

I am the applicant of several publications, many of them on the use of hormones in women.

I direct a team that develops hormones for use in contraception and menopause.

I am a co-inventor of the captioned application.

I have read the prior art documents cited against the present application and I am of the opinion that they do not suggest the claimed method of treating estrogenic deficiencies in women.

I present hereafter the arguments which sustain my opinion.

1) Fraser (Maturitas 1989) does not suggest to use nomegestrol acetate in HRT

Fraser describes :

- **A clinical trial which had a short duration** : the aim of the study was to evaluate the effect of several doses of nomegestrol acetate on endometrium with histological and biochemical methods ; for this reason, women were treated for only 4 lunar calendars. A secretory transformation of endometrium followed by a withdrawal bleeding was observed in all cases **(Table 1)** but the endometrial effects of a long-term continuous estradiol (E2) / nomegestrol acetate treatment are not known.

- **A clinical trial using an unusual sequential HRT (Fig. 1):** nomegestrol acetate was given in a sequential manner (12 days a cycle), i.e. with interruption, and estrogenic stimulation, obtained with E2 subcutaneous implants, was continuous without treatment-free period and induced very high E2 plasma levels (see below). Consequently, it was an unusual design for a sequential HRT combination ; it was only a pharmacological model to check the short term effect of different doses of nomegestrol acetate on endometrium. Even if a regular withdrawal bleeding was observed, it is not possible to conclude, from this trial, that NOMAC could be used in HRT.

- **A clinical trial where women of the same group, receiving the same dose of nomegestrol acetate, had very different E2 plasma levels (Table 2):**

  Estradiol plasma levels did not fit with those usually obtained in HRT.

  No conclusion can be drawn as to the long-term effect of nomegestrol acetate on the endometrium.

- **A clinical trial which did not take into account vasomotor symptoms** which are the major indication for HRT.

- **A clinical trial with a high number of drop-out**
  There were 6 drop-out from 36 patients, ie 17%, during a clinical which only lasted for 4 menstrual cycles. This unusual high drop-out rate came from numerous adverse effects like bleeding and, very often, nausea, headackes, irritability and mood swings. The frequency of these adverse effects shows that the E2/ nomegestrol acetate combination given by Fraser was not suitable for HRT.

In conclusion, Fraser

shows that nomegestrol acetate induces a secretory endometrial transformation in all women

but because
- the clinical trial duration was short,
- the effects on climacteric symptoms were not evaluated
- estrogenic stimulation was continuous, very strong and different from one woman to another
- there were numerous adverse effects and numerous drop-out, making the studied treatment not suitable for long-term therapy of postmenopausal women

the skilled man would not have considered using a combination of nomegestrol acetate and an estrogen for the treatment of estrogenic deficiencies in women, a fortiori a combination to be continuously administered.

2) Plunkett (USRe 36,247) fails to disclose Nomegestrol acetate as progestin and the properties thereof

Plunkett is relied upon for teaching a continuous method of administering a progestin and an estrogen. Plunkett does not disclose nomegestrol acetate, as acknowlegded by the Examiner.

As pointed out during the interview held on June 25, 2002, nomegestrol acetate exhibits specific properties:

❶ Nomegestrol acetate has an original pharmacological profile which is not shared by any synthetic progestin (Table 3)

It is a potent progestin when given by the oral route
It is devoid of any residual androgenic activity
It is devoid of any residual estrogenic activity
It is devoid of any residual gluco-corticoid activity
It is devoid of any residual mineralo-corticoid activity
It has a strong antiestrogenic effect
It has a strong antiandrogenic effect
It has a strong antigonadotropic effect

❷Progestins continuously given with an estrogen induce an endometrial atrophy.

After the issue of the Plunkett's patent, nomegestrol acetate was shown to have a different effect on endometrium **(Fig 2)**; this effect is characterized by a dissociation between anti-estrogenic and progestagen activity : at low doses, the anti-estrogenic effect is predominant and endometrium is atrophic ; at high doses, the progestagen effect is predominant and the endometrium is secretory. Unexpectedly, even with high nomegestrol acetate doses, a large majority of women are amenohrreic **(Fig 2).** This is a characteristic of nomegestrol acetate, never described for other progestins, which can bring clinical advantages, especially in term of acceptability of treatment and consequently compliance, due to an increase of the percentage of no-bleeding pattern.

The skilled man would not have been motivated to use a progestin and an estrogen continuously as taught by Plunkett and to use nomegestrol acetate as progestin because Fraser does not provide any incentive to do so. In addition, the effects of nomegestrol acetate on the endometrium are surprising and unexpected when taken in the light of the cited prior art.

3) Lanquetin (US 5,891,867) does not teach the method claimed in the present application

For reasons already of record, Lanquetin does not teach a method of continuously (i.e. without interruption) administering a progestin and an estrogen. Indeed, Lanquetin teaches a trisequential treatment, with first estradiol alone, then with the estradiol/nomegestrol acetate combination and then with a placebo. This trisequential method results in menstrual bleeding and reproduces in post menopausal women the woman's normal cycle.

In contrast, the method claimed in the present application relates to the administration of both estradiol and nomegestrol acetate given simultaneously with no interruption and avoids menstrual bleeding (no bleeding pattern).

Table 1 : Clinical and endometrial differences between Fraser publication and Lanquetin US Patent n° 5,891,867 vis-àvis current application n° 284,147

	FRASER publication	Lanquetin's patent US Patent 5,891,867	Application N° 284,147 (GEI-067)
Treatment regimen	Sequential treatment	Sequential treatment	Continuous treatment
Menstrual Cycle	Regular	Regular	Absent
Bleeding	Withdrawal bleeding	Withdrawal bleeding	No bleeding
Endometrium	Secretory	Secretory	Atrophic/Secretory depending on dose

Table 2 : Fraser's publication: mean E2 plasma levels (pmol/l) in women of each group

NOMAC dose	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
0.5	830	**1837**	451	1350	793	711	1235	1012	708	581	**284**	919
1	998	590	922	791	1600	364	630	1250	**1525**	**202**	556	673
2.5	830	**1837**	451	1350	793	711	1235	1012	708	581	**284**	919

Table3 : comparison of pharmacological profile of nomegestrol acetate and other progestins

NOMAC	OTHER PROGESTINS	
	Progesterone derivatives	19-nor testosterone derivatives
Strong progestagen activity	Strong progestagen activity except progesterone	
without androgenic residual effects without estrogenic residual effects without gluco-corticoid residual effects without deleterious metabolic effects	with or without androgenic residual effects without estrogenic residual effects with or without gluco-corticoid residual effects with or without deleterious metabolic effects	with androgenic residual effects with estrogenic residual effects with gluco-corticoid residual effects with deleterious metabolic effects
Strong antigonadotropic activity	Only slight antigonadotropic activity	Strong antigonadotropic activity

Figure 1

DIFFERENCES between Lanquetin's US patent 5,891,867, Fraser's Publication and Current application n° 284,147

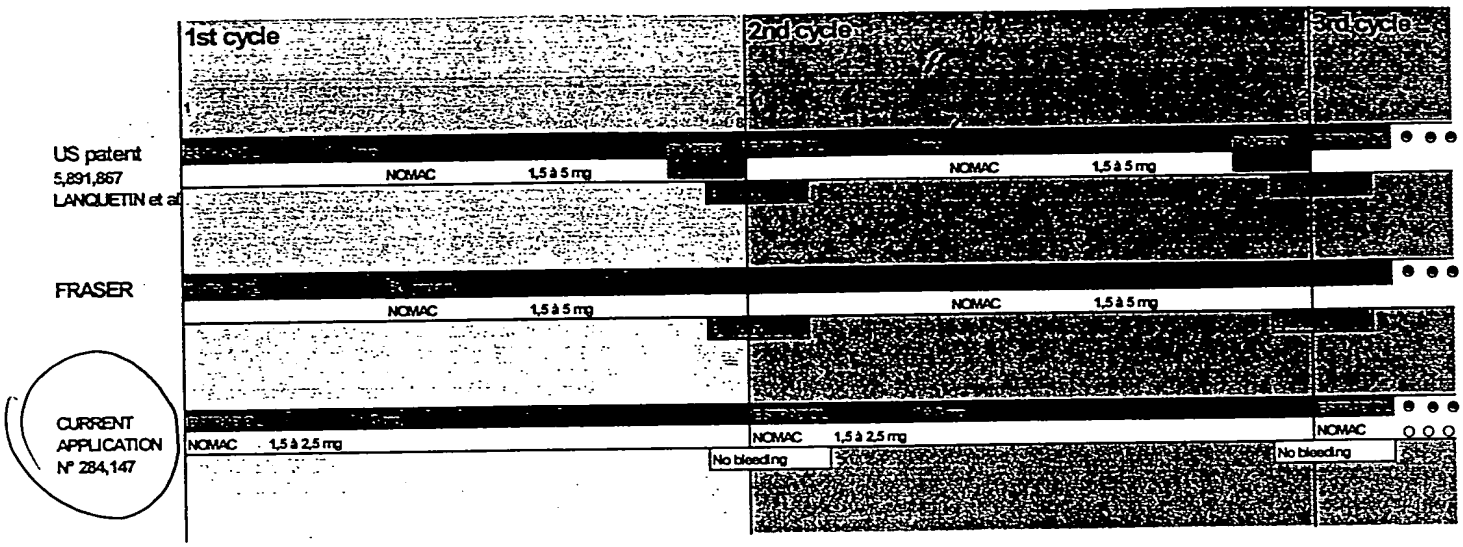
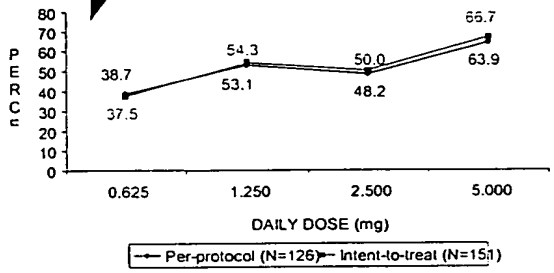


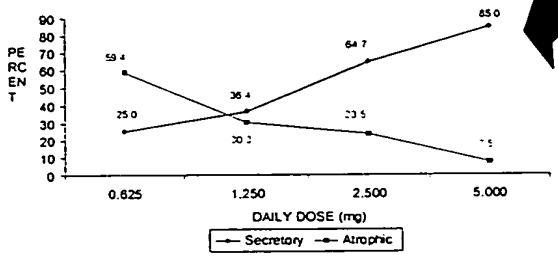
Figure 2 : Endometrial effects of E2/nomegestrol acetate continuous combination

Clinical examples

151 postmenopausal women treated for 6 months)

Dose E2V mg - NOMAC mg	2.0 0.625	2.0 1.25	2.0 2.5	2.0 5.0
Number of patients	37	37	38	38
Amenorrhea (%)	38.7	54.3	50.0	66.7
Secretory endometrium (%)	25.0	36.4	64.7	85.0
Atrophic endometrium (%)	59.4	30.3	23.5	7.5

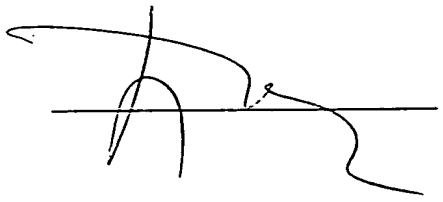




I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 25th day of June 2003

Jean-Louis THOMAS



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CHAPTER 10

Estrogen Replacement and Coronary Heart Disease

Elizabeth Barrett-Connor, M.D.
Trudy L. Bush, Ph.D.

Myocardial infarction is uncommon in premenopausal women in the absence of some predisposing condition such as diabetes or familial hypercholesterolemia. However, women who are oophorectomized before the age of natural menopause appear to have an increased risk of atherosclerosis. These observations suggest that endogenous estrogen is protective: if so, exogenous estrogen as partial replacement therapy for loss of ovarian function might be protective also. The implications of this possible benefit are large: coronary heart disease is far and away the leading cause of death in postmenopausal women.

We review here selected clinical data with regard to the effect of estrogen replacement therapy on heart disease risk factors and observational studies with regard to estrogen replacement therapy and heart disease. Because sequential progestin is now frequently added to estrogen therapy (to reduce the risk of endometrial cancer), the effects of estrogen alone are contrasted with estrogen plus progestin regimens wherever data permit.

THE HORMONES

Estrogen

Some of the discrepancies in the literature about the effects of estrogen replacement therapy on heart disease risk factors result from a failure to consider the different estrogens and progestins used. Equivalent effects on the reproductive system and/or menopause symptoms do not necessarily equate with similar effects on heart disease risk factors. For cyclic or sequential regimens, the timing of the measurements or venipunctures may be important also.

Estrogens used for therapeutic purposes can be divided into three major classes: (1) the "natural" steroidal estrogens such as conjugated equine estrogens (Premarin), 17-β-estradiol (Estrace), and estrone sulfate (Ogen); (2) the synthetic steroidal estrogens, including ethinyl estradiol (Estinyl) and mestranol; and (3)

the synthetic nonsteroidal formulations, including stilbestrol and diethylstilbestrol (DES). "Natural" estrogens are distinguished from synthetic ones by the fact that their chemical structures are found in nature (although not necessarily in humans), whereas the chemical structures of the synthetic agents are man-made.

Unlike the formulations used for contraceptive purposes, in which synthetic estrogens are used exclusively, nearly all of the estrogens prescribed for menopausal symptoms are natural. In the United States, Premarin alone accounts for 75 percent of all prescriptions, and other natural agents account for approximately 15 percent of use. Synthetic estrogens, particularly ethinyl estradiol, make up the remainder of use for menopausal replacement therapy.

The relative potency of synthetic compared with natural compounds is variable and highly dependent on the target tissue. Thus, it is difficult to assess in any systematic manner. If the ability to suppress ovulation is considered, the potency of the usual dose of Premarin (0.625 mg) is between 10 and 40 percent that of the usual doses of ethinyl estradiol (30 to 50 μg). The synthetic estrogens also appear to have greater impact than natural agents on coronary risk factors, including blood pressure, lipids and lipoproteins, glucose tolerance, and clotting parameters. However, insufficient data exist to address adequately these latter relationships.

Progestins

Progestins can be grouped into three categories: two types of synthetic formulations, and natural progesterone. The two major classes of synthetic progestins available are the 19-nor-testosterone (19-nor) derived hormones, which include norethindrone (norethisterone), norethindrone acetate (Norlutate), and levonorgestrel (Ovrette), and the C-21 progestins derived from 17-alpha hydroxyprogesterone, including hydroxyprogesterone caproate (Prodrox) and medroxyprogesterone acetate (Provera). The 19-nor agents are used exclusively in combination-contraceptive therapy, and have been shown to have strong androgenic properties. The 17-alpha agents, in particular Provera, are usually used in menopausal replacement therapy and are considered less androgenic than the 19-nor agents. In the United States, approximately 90 percent of women receiving hormonal replacement therapy use Provera, and the remaining 10 percent use norethindrone acetate. Recently, natural progesterone has been micronized for oral use and appears to have little or no androgenic effect. It has not been studied extensively and is not commercially available in the United States.

Although some progestins do have estrogenic effects, the major metabolic effects of progestational agents appear to be dependent on estrogen priming; that is, progestins behave primarily as antiestrogens by blocking the synthesis of new cytoplasmic estrogen receptors. Because of this metabolic symbiosis, biologic effects of unopposed progestins have not been systematically evaluated.

A variety of studies have evaluated the effects of various estrogen formulations and regimens in relation to risk factors. However, almost all of the estrogen–heart disease studies have involved estrogen replacement therapy with unopposed (i.e., without progestin) conjugated equine estrogen (Premarin). Extrapolation of these study results to other estrogens or to estrogen plus progestin regimens is not necessarily valid.

ESTROGEN REPLACEMENT THERAPY AND HEART DISEASE RISK FACTORS

Obesity

Cross-sectional population-based data suggest that women given postmenopausal estrogens are leaner than those not so treated,[1,2] but do not exclude the possibility that thin women are more likely to be prescribed estrogen replacement therapy. The few trials of sufficient duration to address the effect of estrogen replacement therapy on weight suggest that estrogen may modify weight gain. Hart and coworkers[3] reported that overweight oophorectomized women treated with 40 μg/day of mestranol for 1 to 7 years tended to lose weight, whereas overweight placebo recipients gained weight; no change in weight was noted in normal-weight women with or without estrogen replacement therapy. Similarly, Jensen and coworkers[4] reported that body weight did not change in postmenopausal women treated for 1 or 2 years with percutaneous estrogen, but there was significant weight gain in women treated with placebo.

Blood Pressure

Contrary to the literature on oral contraceptives, most studies suggest that the majority of estrogen-treated postmenopausal women experience a reduction in blood pressure with estrogen replacement therapy. Differences in reported estrogen–blood pressure associations may reflect different hormone products, doses or duration of use, small sample size, subject selection, and/or the limited number of blood pressure measurements made before and during treatment. In addition, observations often were made by persons without training in standardized blood pressure measurement, and relatively few investigators considered the effect of pretreatment blood pressure on the results.

In one of the better clinical trials, Lind and associates[5] recruited 56 women aged 49 to 55 years from general practices into a randomized placebo-controlled study of three available forms of oral estrogen (conjugated equine estrogen, 1.25 mg/day; piperazine estrone sulfate, 1.5 μg/day; and estradiol valerate, 2 mg/day), each given with or without the progestin norgestrel, 0.5 mg. Although there were relatively few women in each treatment group, each had several measurements of blood pressure before, during, and after hormone replacement therapy. Overall, these women had statistically significant decreases in both systolic and diastolic blood pressures, which returned to pretreatment levels after replacement therapy was discontinued. No difference in response was mentioned when estrogen was prescribed with a progestin. Approximately one-fourth of all treated women had no change in their blood pressure.

In another randomized clinical trial, Luotola[6] treated 20 normotensive and 20 hypertensive women, aged 41 to 55, who were seen for menopause symptoms with 2 or 4 mg/day of 17-β-estradiol. In this cross-over design, both normotensive and hypertensive women had significant reductions in systolic and diastolic blood pressures, which reversed during the placebo period. These blood pressure changes correlated significantly with changes in serum estrone. No other clinical or physiological characteristic distinguished these women from the few patients who had a modest *rise* in blood pressure with estrogen replacement therapy or explained the fall in blood pressure in the majority.

A third randomized clinical trial, by Wren and Roultedge,[7] included a much larger number of patients referred from a menopause clinic, but obtained only a single pre- and post-treatment blood pressure. Each patient received 24 days of one of two oral estrogens and 0.03 mg of levonorgestrel on days 15 to 24. There was a consistent decrease in both systolic and diastolic blood pressures in the 184 women assigned to piperazine estrone sulfate, 0.625 to 1.25 mg/day. No blood pressure change was observed in 144 women who received conjugated equine estrone in doses of 0.3 to 1.25 mg/day. In this study, no dose response effect was seen with either product.

The observation that oral, but not percutaneous, estrogen is associated with an increase in renin substrate is probably unrelated to the observed blood pressure effects. The long-term effect of oral and percutaneous estrogen replacement therapy on blood pressure and plasma renin was studied by Hassager and associates[8] in a 2-year placebo-controlled study of 110 early postmenopausal women. In this study, women were allocated to one of four treatment groups: oral cyclical combination of 2 mg estradiol valerate and cyproterone acetate; oral placebo; percutaneous 17-β-estradiol, supplemented by 200 mg of oral progesterone during the second year; and percutaneous placebo cream. Systolic and diastolic pressures remained unchanged in both estrogen treatment groups, whereas a significant increase in diastolic blood pressure was observed in both placebo groups. Plasma renin substrate increased during oral treatment with estradiol but was unchanged with percutaneous estradiol; no correlation was found between blood pressure and plasma renin substrate.

Synthetic progestins have been implicated in hypertension from the studies of oral contraceptives. However, natural progesterones have vasodilating properties. In a double blind study of four hypertensive postmenopausal women by Rylance and colleagues,[9] micronized progesterone was alternated every 2 weeks with placebo, and the dose was increased from 200 mg/day to a total of 600 mg/day. There was a significant fall in blood pressure while the women were receiving progesterone, but not while taking placebo. The maximum fall coincided with the highest dose, an average of 19.7 mmHg systolic and 9.6 mmHg diastolic. In the aforementioned study by Hassager and colleagues,[8] however, diastolic and systolic blood pressures and renin substrate were not influenced by the addition of micronized progesterone to oral or percutaneous estrogen.

These studies suggest that estrogen replacement therapy has no adverse effects on blood pressure levels in the majority of women, in whom it may, in fact, be hypotensive.

Clotting Factors

Large doses of estrogen may alter clotting factors and increase the risk of thrombotic events in premenopausal women. However, studies of clotting and estrogen replacement therapy in postmenopausal women are rare. In an older report, Bonnar and coworkers[10] performed serial studies of coagulation factors in three small groups of women with menopausal symptoms. Eleven women who received large doses of mestranol (up to 50 μg) and norethisterone, 1.5 mg/day, had increases in Factors VIII, IX, and X and a decrease in antithrombin III. Both estradiol valerate (2 mg/day) and conjugated equine estrogen (1.25 mg/day) increased Factor VII and X complex, but only the former increased Factors II and X. Neither had a measurable effect on antithrombin III. Hart and coworkers[3]

compared clotting function in 146 women taking mestranol and 121 taking placebo for 1 to 7 years. There was no significant difference in prothrombin time, partial thromboplastin time, or Factor X, but 24 patients taking mestranol (in an average daily dose of 25 μg) had elevated Factor VIII compared with 7 women in the placebo group.

In more recent reports, there is less evidence of abnormal clotting with estrogen replacement therapy. In the randomized clinical trial reported by Lind and associates,[5] none of the six estrogen replacement therapy regimens (detailed above under Blood Pressure) resulted in a change in antithrombin III, prothrombin time, partial thromboplastin time, fibrogen degradation products, Factor V, VIII, or X, platelet count, or platelet aggregation. More recently, Chetkowski and colleagues[11] reported no change in fibrinogen A, high molecular weight fibrogen, antithrombin III level, or activity in 23 women randomly assigned to up to 200 μg/day of transdermal estradiol or up to 1.25 mg/day of conjugated equine estrogen.

The earlier reports of adverse coagulation effects associated with hormone replacement may have been due to a very high dose of estrogen or the concurrent use of a progestin. No hormonal effect on blood coagulation is the rule with current regimens.

Lipids and Lipoproteins

In contrast to the paucity of studies of estrogen replacement therapy on obesity, blood pressure, and coagulation, multiple studies of estrogen replacement therapy with regard to lipids and lipoproteins have been reported. Despite the large number of studies, repeated investigations of the same estrogen or estrogens in the same dose and regimen to women with similar treatment eligibility criteria are rare, and this plus small sample size in many studies precludes a meaningful comparison or synthesis of these data. The studies briefly reviewed here were selected because of superior design, because of illustration of a particular point, or because they are the only available studies of a particular regimen.

A great many studies suggest that estrogen replacement therapy has little or no effect on total plasma cholesterol and a variable effect on triglycerides.[12] The triglyceride elevating effect of synthetic and equine estrogens is presumably due to increased production. As reviewed elsewhere,[13] androgenic progestins such as norethindrone probably lower triglyceride in women whose hypertriglyceridemia is due to increased production. The thesis that nonalkylated estrogens like estradiol valerate have no effect on triglyceride or very low density lipoprotein (VLDL)[14] has not been confirmed by all investigators.[15] Since the relationship of triglyceride to coronary heart disease risk is controversial,[16] and any effect may be mediated via the inverse association of high density lipoprotein (HDL) with triglyceride, the remainder of this review will focus on the lipoproteins. Obviously, the proportionate effects of estrogen replacement therapy on HDL and low density lipoprotein (LDL) will also determine to a large extent the overall effect on total cholesterol.

Since the 1952 report by Barr and coworkers[17] that oral estrogen therapy increases alpha lipoprotein (HDL) and decreases beta lipoprotein (LDL), nearly all studies have confirmed that unopposed oral estrogen causes lower LDL and higher HDL levels, i.e., a favorable lipoprotein ratio with regard to heart disease risk. The range of reported responses probably reflects the effect of different dose,

drug, and duration of therapy, cyclic versus continuous use, and/or subject selection, sampling frame, and sampling schedule. For example, the use of conjugated equine estrogens, the most popular non-contraceptive estrogen in the United States, has been associated with lower LDL and higher HDL levels in most studies. As reviewed by Bush and Miller,[12] the broad range of reported values includes a 0 to 26 percent increase in HDL and a 4 to 19 percent decrease in LDL; after correcting for the size and duration of the study, at a 0.625-mg daily dose, HDL levels are increased by 10 percent and LDL levels are decreased by 4 percent. With a higher 1.25-mg dose, HDL increased by 14 percent and LDL decreased by 8 percent.

In contrast to the general agreement that unopposed oral estrogens raise HDL and lower LDL cholesterol, there is more controversy about the effect of parenteral and percutaneous estrogen. Reported differences in lipoprotein levels are not entirely explained by dose or route of administration. Fletcher and coworkers[18] studied 34 bilaterally oophorectomized women who received 50 mg 17-β-estradiol by subcutaneous implant every 6 months. Compared with 67 untreated oophorectomized women, there was no significant difference in HDL (including subfractions) or LDL levels in the treated women after 6 months or again after 3 years, despite their high serum estradiol levels. In another study, however, there was a significant fall in LDL and rise in HDL levels 14 weeks after implantation of a larger dose of 100 mg of 17-β-estradiol in eight oophorectomized women.[19] With transdermal estradiol in doses up to 200 μg/day, Chetrowski and associates[11] reported no significant change in LDL and HDL. However, Jensen and associates[4] treated 45 postmenopausal women for 2 years with either 3 mg of percutaneous estradiol or placebo. In this study, percutaneous estradiol significantly reduced LDL but had no effect on HDL. (Addition of micronized progesterone did not ablate these changes and may have raised HDL slightly.) Conjugated equine estrogens given vaginally in doses up to 2.5 mg are reported to have no effect on lipoproteins.[20]

Several investigators have attempted to determine the effect of an added progestin on estrogen-associated lipoprotein changes. In one of the first clinical trials designed to specifically study the effect of different progestins on lipoproteins during postmenopausal therapy, Hirvonen and colleagues[21] treated 18 postmenopausal women with estradiol valerate 3 mg/day for 3 weeks; they were then assigned (in groups of six) to two cycles of norethindrone acetate 10 mg/day, medroxyprogesterone 10 mg/day, or norgestrel 0.5 mg/day. HDL cholesterol decreased by 20 percent in those receiving estradiol plus norethindrone or norgestrel but did not change significantly in the group receiving estradiol plus medroxyprogesterone.

Farish and coworkers[22] treated 21 oophorectomized women with conjugated equine estrogen alone and 21 women who had a natural menopause with conjugated equine estrogen 0.625 mg, plus norgestrel 0.15 mg/day, for the last 12 days of each treatment cycle. Women treated with the unopposed estrogen had a significant increase in HDL, especially HDL_2, and a significant decrease in LDL, whereas those who received both hormones showed only a significant decrease in LDL.

Ottosson[23] studied 140 women, aged 32 to 70, who were treated with three cycles of unopposed oral estrogen followed by the sequential addition of a progestin for the next three cycles. HDL_2 levels were increased by 29 percent on 10 μg of ethinyl estradiol compared with 16 percent on 2 mg/day of estradiol valer-

ate. The addition of synthetic progestin decreased HDL and HDL_2 levels; for example, estradiol valerate given with sequential levonorgestrel reduced HDL_2 by 28 percent, and given with sequential medroxyprogesterone, by 17 percent. In contrast, 200 mg of micronized progesterone had no apparent effect on plasma HDL.

In one of the largest studies, Christiansen and associates[24] randomly allocated 177 postmenopausal women aged 44 to 59 to one of the three daily doses of micronized estrogen in combination with norethisterone 1 mg/day, given from the 13th to 23rd of the month. Over a 3-year period, blood samples obtained every 3 months during the progestin phase showed a 10 to 13 percent reduction in total cholesterol on the high (4-mg) estrogen dose, a 5 percent reduction on the medium (2-mg) dose, and a 3 percent reduction on the low (1-mg) dose. Reduction in total cholesterol was due entirely to reduced LDL cholesterol; there were no significant changes in HDL.

Lipoprotein levels may vary with the timing of the blood sampling in estrogen-progestin treated women. Teichmann and associates[25] studied 20 oophorectomized women before and after 1 year of treatment with 1.25 mg of conjugated estrogen and 5 mg of medroxyprogesterone in a cyclic protocol. Blood obtained on the last 3 days of the cycle showed a significant increase in HDL and a significant decrease in LDL.

Jensen and coworkers[26] studied 30 women aged 45 to 54 who were randomly allocated to high, medium, or low dose micronized estrogen, sequentially combined with norethisterone 1 mg/day, given on days 13 to 22 of two consecutive cycles. Blood for lipid and lipoprotein analysis was obtained twice a week in these women. The lowest total cholesterol was achieved during the estrogen-progestin days, but the lowest HDL was observed during the first 14 days, when estrogen was given alone.

Vejtorp and coworkers[27] randomly allocated 30 perimenopausal women from general practice to receive sequential therapy with either estradiol valerate 2 mg/day and norgestrel 0.5 mg/day, or micronized estradiol 2 mg/day and medroxyprogesterone 10 mg/day. Blood obtained during the estrogen phase showed no difference in lipoprotein level expressed as a percentage of pretreatment level, but blood obtained in the progestin phase showed the percentage of HDL (and VLDL) to be significantly higher in women treated with estradiol plus medroxyprogesterone.

In summary, it appears that unopposed oral estrogen provides an improved lipoprotein ratio, with a more striking effect on HDL than LDL. Results are less consistent with estrogen given by other routes or in conjunction with a progestin. If a progestin is added, the least androgenic preparation and the lowest dose known to inhibit endometrial hyperplasia should be used.

EXOGENOUS ESTROGEN USE AND CORONARY HEART DISEASE

Background

In the early 1960s the concept of long-term estrogen replacement therapy ("feminine forever") was popularized by Wilson and Wilson. From that time until about 1975, millions of American women took unopposed estrogen therapy for prolonged periods, allowing for the observations of long-term sequelae. In

1975, the *New England Journal of Medicine* published two articles showing that unopposed estrogen therapy increased the risk of endometrial carcinoma. Since the publication of those and subsequent articles, unopposed estrogen therapy became less popular. Toward the end of the 1970s, there was sufficient evidence to show that the addition of a progestational agent to an estrogen regimen could negate the increased risk of endometrial carcinoma. Subsequently, most women with intact uteri are prescribed estrogens cycled with progestins.

With the exception of one study reported below (Nachtigall et al), all of the studies reviewed preceded the widespread use of estrogen plus progestin in postmenopausal women. Thus, the vast majority of hormone users were women who took unopposed estrogens. Therefore, the question of the effects of estrogen/progestin therapy on risk of coronary heart disease has yet to be addressed, and the results reviewed here cannot be equated with those that would follow estrogen cycled with a progestin.

Study Results: Overview

Currently there are 19 studies reported (Table 10–1) that have evaluated the effects of estrogen replacement therapy on risk of coronary heart disease.[24–46] Of these 19 reports, 10 are cohort studies,[37–46] 8 are case-control studies,[29–36] and 1 is a randomized clinical trial.[28] Eleven of the 19 reports, including the clinical trial, 8 of the 10 cohort studies, and 2 of the 8 case-control studies, found that women using estrogens had a reduction in the risk of coronary heart disease of 50 percent or greater. Four of the studies (one cohort, three case-control) reported a reduction of risk of coronary disease of 30 to 50 percent in estrogen users. Two reports (both case-control) found no difference in risk for estrogen users, and two studies (one cohort and one case-control) actually found an increased risk of heart disease in women reporting estrogen use.

The variability of these results may be explained by a variety of factors that differed among the studies, including actual study design, study population, age of study subjects, definition of estrogen use, and endpoints considered. Nonetheless, it seems clear that the vast majority of studies to date (~80 percent) have found that estrogen use protects against coronary disease. This protective effect is biologically plausible, inasmuch as estrogens have marked beneficial effects on lipids and lipoproteins, and apparently do not adversely affect other risk factors for CHD.

Study Results: Review of Studies

Clinical Trials

Only one clinical trial of estrogen use and risk of coronary disease has been published. Nachtigall and colleagues[28] reported in 1979 the results of a double-blind randomized trial of 10 years' duration. Participants were residents of a long-term care chronic disease hospital, and most suffered from chronic conditions such as diabetes mellitus, neurologic disorders, and arteriosclerosis. Eighty-four age- and condition-matched pairs of women were selected for the trial, and one woman of each pair was randomly assigned to take 2.5 mg of Premarin daily and 10 mg of Provera for 7 days a month. The other half of the pair took placebos. At the end of 10 years of follow-up, women assigned hormonal therapy, compared

Table 10–1. Summary of Studies of Replacement Estrogen and Cardiovascular Disease

Study	Study Design	Population Size	Endpoints	Relative Risk	p Value
Nachtigall et al[28]	Randomized trial	84 pairs	Fatal/non-fatal MI	0.33	p >.05
Talbott et al[29]	Case-control	64 cases 64 controls	Sudden death	0.34	p >.05
Ross et al[30]	Case-control	133 cases 133 controls	Fatal CHD	0.43	p <.01
Szlko et al[31]	Case-control	36 cases 39 controls	Non-fatal MI	0.61	p >.05
Adam et al[32]	Case-control	76 cases 151 controls	Fatal MI	0.65	p >.05
Pfeffer et al[33]	Case-control	185 cases 511 controls	Fatal/non-fatal MI	0.68	p >.05
Rosenberg et al[34]	Case-control	336 cases 6,730 controls	Non-fatal MI	0.97	p >.05
Rosenberg et al[35]	Case-control	477 cases 1,832 controls	Non-fatal MI	1.00	p >.05
Jick et al[36]	Case-control	17 cases 34 controls	Non-fatal MI	7.5	p <.05
Lafferty et al[37]	Cohort	124 women	Fatal/non-fatal MI	0.16	p = .05
MacMahon[38]	Cohort	1,891 women	All CVD	0.30	NA
Stampfer et al[39]	Cohort	32,317 women	All CVD	0.30	p <.01
Hammond et al[40]	Cohort	610 women	All CVD	0.33	p <.01
Potocki et al[41]	Cohort	198 women	All CVD	0.33	NA
Bush et al[42]	Cohort	2,270 women	CVD mortality	0.34	p <.05
Burch et al[43]	Cohort	737 women	Fatal CHD	0.43	p <.05
Petitti et al[44]	Cohort	16,638 women	CVD deaths	0.50	p <.05
Henderson et al[45]	Cohort	7,610	Fatal/non-fatal MI	0.54	p <.05
Wilson et al[46]	Cohort	1,234 women	All CVD	1.76	p <.05

MI = myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease; NA = not available.

with the placebo group, had a relative risk 0.33 for fatal and nonfatal myocardial infarction. The non-representativeness of the study subjects, the absence of data showing the success of randomization and the distribution of other medication use, and the small sample size all limit the conclusions that can be drawn from this single clinical trial.

Case-Control Studies

Of the eight case-control studies reported, five[29–33] show relative risks for heart disease among estrogen users to be between 0.33 and 0.68 that of non-users,

two showed no effect of estrogen use,[34,35] and one reported an increased risk for estrogen users.[36]

Both of the case-control studies that found no effect of estrogen therapy on heart disease were analyses done by Rosenberg and colleagues.[34,35] In their first report from the Boston Collaborative Drug Surveillance Program (1976), they compared estrogen use in 336 women between the ages of 40 and 75 years with non-fatal myocardial infarction with estrogen use in 6730 controls. They initially found a crude odds ratio of 0.47 for estrogen use. However, after adjusting for a wide variety of factors, including religion, hospital site, and coffee consumption, the odds ratio was found to be 0.97.

In their second report, they compared estrogen use in women aged 30 to 49 years admitted with non-fatal myocardial infarction to coronary care units in 155 U.S. hospitals with estrogen use in 1832 controls. The odds ratio for recent estrogen use was found to be 1.0, and that for past use was 1.2. The generalizability of these findings is unknown, inasmuch as women between the ages of 30 and 49 years are at very low risk of both estrogen replacement therapy and myocardial infarction.

The case-control study that reported an increased risk for estrogen users was reported by Jick and associates in 1978.[36] In this small study with 17 cases of non-fatal myocardial infarction and 34 controls, they found an odds ratio of 7.5 for estrogen use. However, they had initially identified 107 cases of myocardial infarction but were able to include only 17 in the analyses; additionally, 16 of 17 women were smokers. These serious methodologic problems make the results of this analysis questionable.

Cohort Studies

With the exception of the Framingham Study, all of the other nine cohort studies to date have found a protective effect of estrogen use on coronary heart disease. The relative risks reported have ranged from 0.16 to 0.54. Five of these major studies, including Framingham, are reviewed below.

THE NURSES STUDY. Stampfer and colleagues[39] surveyed by mail over 120,000 female nurses who were aged 30 to 55 years in 1976. At that time, baseline information on hormone use and other coronary risk factors was ascertained. Over 92 percent of the initial cohort was located via questionnaire in 1978 and 1980, and risk factor status and incident coronary disease were gathered at these times. The incidence of non-fatal myocardial infarction and fatal heart disease was then calculated for women who had never used postmenopausal hormones, for women who had ever used them, and for women who were currently using them at the baseline survey. Compared with never-users, ever-users had a relative risk of 0.5 for coronary disease, and current users had a relative risk of 0.3. These reductions in risk are statistically significant ($p < 0.01$). Statistical adjustment for reported smoking, hypertension, diabetes, hypercholesterolemia, family history of heart disease, past oral contraceptive use, and obesity did not alter the risk estimates. The authors conclude that their data support the hypothesis that postmenopausal estrogen use reduces the risk of coronary heart disease.

This study can be criticized because it relies almost entirely on self-report of risk factors, including hormone use. Such misclassification could bias the risk estimates. Nonetheless, the very large numbers of postmenopausal women ($N = 32,317$) and person-years of follow-up ($PY = 105,786$) mean that any random misclassification bias should not appreciably affect the results.

LEISURE WORLD. Henderson and associates[45] mailed a questionnaire in 1981 to all residents of Leisure World, Laguna Hills, an upper-middle-class retirement community near Los Angeles. Over 60 percent of the population responded, and this identifed cohort was enrolled in a mortality follow-up study. Follow-up includes all hospital admissions to the three hospitals serving the area and all deaths reported to the county health department. After 2 years, less than 1 percent of the 7610 women had been lost to follow-up.

After 3 years of follow-up, 56 deaths due to acute myocardial infarction were observed. The risk of death from myocardial infarction in ever-users of estrogens compared with never-users was 0.54. This finding is statistically significant ($p < 0.01$) and not influenced by previous history of heart attack or angina, hypertension, body weight, hysterectomy status, or smoking. The authors conclude that the finding of a protective effect of estrogen use from death from acute myocardial infarction is consistent with secular changes observed in death rates from MI. That is, the decline in cardiovascular mortality rates since 1960 is consistent with the increased use of estrogen since that time.

WALNUT CREEK. Petitti and coworkers[44] followed a group of 16,638 women, aged 18 to 54, who were members of The Northern California Kaiser-Permanente Medical Care Program. These women had been recruited into a study of contraceptive drug use in the late 1960s and early 1970s and provided data on all hormone use at entry. Women who had ever used oral contraceptives or who had a history of cardiovascular disease were excluded from the analysis. Mortality rates for all cardiovascular deaths was lower (RR = 0.80) in women reporting any noncontraceptive estrogen use. After statistically adjusting for other cardiovascular risk factors, including age, smoking, alcohol use, body mass, and history of hypertension, the relative risk of cardiovascular disease deaths in users compared with non-users was 0.50. This represents a statistically significant reduction in risk of cardiovascular mortality among estrogen users.

FRAMINGHAM. Wilson and associates,[46] using data gathered previously in the Framingham Heart Study, classified participants as estrogen users if that medication was recorded on their medication form at any of the biennial examinations 8 through 12. Additionally, participants had to be postmenopausal and 50 years of age or older at the 12th examination. A total of 1234 women met these criteria and were then followed for 8 years. Cardiovascular disease occurrence was defined to include all of the following: coronary heart disease, angina pectoris, myocardial infarction, stroke, transient ischemic attack, intermittent claudication, congestive heart failure, coronary death, and sudden death. All cardiovascular disease rates were significantly higher in women who reported any estrogen use. After adjustment for age, blood pressure, body mass, total cholesterol/HDL cholesterol, smoking and alcohol consumption, estrogen users compared with non-users had a relative risk of 1.76 ($p < 0.05$) for all cardiovascular disease. Deaths from all causes were not elevated (RR = 0.97). The authors conclude that estrogen therapy has potential drawbacks, particularly in regard to cardiovascular disease.

The inclusion of a wide variety of endpoints in the definition of cardiovascular disease is troubling and may lead to bias if, for example, a physician may be more likely to diagnose a transient ischemic attack in a woman taking estrogen. Furthermore, the statistical adjustment for the total cholesterol/HDL cholesterol ratio can be viewed as inappropriate, inasmuch as estrogen use both strongly influences these measures and exerts its putative protective effect by this mecha-

nism. A re-analysis of the Framingham data in women aged 50 to 60, using specific endpoints, and 10-year incidence rates and not adjusting for the cholesterol and lipoprotein ratio, has shown that the overall risk of coronary heart disease in estrogen users was approximately half that of non-users. It is difficult to assess the meaning of these discrepant results from the same data. Perhaps additional analyses from this cohort will be forthcoming.

LRC FOLLOW-UP STUDY. Bush and colleagues[42] followed 2270 white women aged 40 to 69 at baseline for an average of 8½ years in the Lipid Research Clinics Follow-Up Study. Estrogen use was defined at one point (between 1972 and 1974), and the endpoint was death from all cardiovascular diseases. Cardiovascular deaths were defined by a mortality classification panel comprising five cardiologists. Follow-up of the participants was virtually complete. After 8½ years, women using estrogens, compared with non-users, had a relative risk of cardiovascular death of 0.34. This reduction in risk is statistically significant ($p < 0.05$) and was not influenced by adjustment for age, smoking, blood pressure, total cholesterol level, alcohol use, body mass, exercise, triglycerides, education, and hysterectomy status. However, adjustment for HDL and LDL cholesterol levels did markedly diminish the protective effect of estrogen use on cardiovascular death. The authors conclude that the protective effect of estrogen on cardiovascular disease death is mediated by increased HDL levels among estrogen users.

CONCLUSIONS

Unopposed estrogen replacement therapy appears to have a beneficial effect on lipoproteins and blood pressures and to be highly protective for the subsequent development of fatal and non-fatal coronary disease in women. Because the vast majority of these studies are observational, the issue of selection bias for estrogen use (i.e., healthier women are more likely to be prescribed estrogen) cannot be laid to rest. However, extensive post-hoc analyses in all of the cohort studies (with the exception of Framingham) reveal no apparent differences in cardiovascular risk between estrogen users and non-users. A randomized clinical trial to address the question of selection bias is probably warranted, although unlikely (owing to feasibility issues).

Perhaps the major unanswered question at this time is whether the use of estrogen cycled with a progestin is as protective against cardiovascular disease as is the use of unopposed estrogen. Currently, the data on the effects of estrogen/progestin formulations on coronary heart disease risk factors are mixed; and unfortunately, data on estrogen/progestin use and risk of actual heart disease are non-existent. However, given the popular current prescribing practices of both cyclic and continuous estrogen-progestin therapy, this question may be addressable in the near future.

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Premarin Intravenous—Cont.

2. *Other possible cancers.* Estrogens can cause development of other tumors in animals, such as tumors of the breast, cervix, vagina, or liver, when given for a long time. At present there is no good evidence that women using estrogens in the menopause have an increased risk of such tumors, but there is no way yet to be sure they do not; and one study raises the possibility that use of estrogens in the menopause may increase the risk of breast cancer many years later. This is a further reason to use estrogens only when clearly needed. While you are taking estrogens, it is important that you go to your doctor at least once a year for a physical examination. Also, if members of your family have had breast cancers, or if you have breast nodules, or abnormal mammograms (breast X rays), your doctor may wish to carry out more frequent examinations of your breasts.

3. *Gallbladder disease.* Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens. Birth-control pills have a similar effect.

4. *Abnormal blood clotting.* Taking estrogens may increase the risk of blood clotting in various parts of the body. This can result in a stroke (if the clot is in the brain), a heart attack (a clot in a blood vessel of the heart), or a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal.

It is recommended that if you have had clotting in the legs or lungs, or a heart attack or stroke, while you were using estrogens or birth-control pills, you should not use estrogens (unless they are being used to treat cancer of the breast or prostate). If you have had a stroke or heart attack, or if you have angina pectoris, estrogens should be used with great caution and only if clearly needed (for example, if you have severe symptoms of the menopause).

5. *Inflammation of the pancreas (Pancreatitis).* Women with high triglyceride levels may have an increased risk of developing inflammation of the pancreas.

Special Warning About Pregnancy

You should not receive estrogen if you are pregnant. If this should occur, there is a greater than usual chance that the developing child will be born with a birth defect, although the possibility remains fairly small. A female child may have an increased risk of developing cancer of the vagina or cervix later in life (in the teens or twenties). Every possible effort should be made to avoid exposure to estrogens during pregnancy. If exposure occurs, see your doctor.

Other Effects of Estrogens

In addition to the serious known risks of estrogens described above, estrogens have the following side effects and potential risks:

1. *Nausea and vomiting.* The most common side effect of estrogen therapy is nausea. Vomiting is less common.

2. *Effects on breasts.* Estrogens may cause breast tenderness or enlargement and may cause the breasts to secrete a liquid. These effects are not dangerous.

3. *Effects on the uterus.* Estrogens may cause benign fibroid tumors of the uterus to get larger.

4. *Effects on liver.* Women taking oral contraceptives develop, on rare occasions, a tumor of the liver which can rupture and bleed into the abdomen and may cause death. So far, these tumors have not been reported in women using estrogens in the menopause, but you should report any swelling or unusual pain or tenderness in the abdomen to your doctor immediately.

Women with a past history of jaundice (yellowing of the skin and white parts of the eyes) may get jaundice again during estrogen use. If this occurs, stop taking estrogens and see your doctor.

5. *Other effects.* Estrogens may cause excess fluid to be retained in the body. This may make some conditions worse, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

Summary

Estrogens have important uses, but they have serious risks as well. You must decide, with your doctor, whether the risks are acceptable to you in view of the benefits of treatment. Except where your doctor has prescribed estrogens for use in special cases of cancer of the breast or prostate, you should not use estrogens if you have cancer of the breast or uterus, are pregnant, have undiagnosed abnormal vaginal bleeding, clotting in the legs or lungs, or have had a stroke, heart attack or angina, or clotting in the legs or lungs in the past while you were taking estrogens.

You can use estrogens as safely as possible by understanding that your doctor will require regular physical examinations while you are taking them, will try to discontinue the drug as soon as possible, and use the smallest dose possible.

Be alert for signs of trouble including:

1. Abnormal bleeding from the vagina.
2. Pains in the calves or chest, or sudden shortness of breath, or coughing blood.
3. Severe headache, dizziness, faintness, or changes in vision.
4. Breast lumps (you should ask your doctor how to examine your own breasts).
5. Jaundice (yellowing of the skin).
6. Mental depression.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

HOW SUPPLIED

Premarin® (conjugated estrogens tablets, USP) tablets for oral administration.
Premarin® Vaginal Cream—Premarin® in a nonliquefying base, designed for vaginal use.
Premarin® Intravenous—Premarin® specially prepared for intravenous and intramuscular use.
Manufactured by:
Ayerst Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

PREMARIN® Rx
[prĕm 'a-rĭn]
(conjugated estrogens tablets, USP)

Caution: Federal law prohibits dispensing without prescription.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

DESCRIPTION

Premarin (conjugated estrogens tablets, USP) for oral administration contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin. Tablets for oral administration are available in 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg strengths of conjugated estrogens.

Premarin Tablets contain the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide.

— 0.3 mg tablets also contain: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Yellow No. 6; these tablets comply with USP Drug Release Test 1.
— 0.625 mg tablets also contain: FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40; these tablets comply with USP Drug Release Test 1.
— 0.9 mg tablets also contain: D&C Red No. 6, D&C Red No. 7; these tablets comply with USP Drug Release Test 2.
— 1.25 mg tablets also contain: black iron oxide, D&C Yellow No. 10, FD&C Yellow No. 6, talc; these tablets comply with USP Drug Release Test 3.
— 2.5 mg tablets also contain: FD&C Blue No. 2, D&C Red No. 7, talc; these tablets comply with USP Drug Release Test 3.

CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes.

Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth ar development of the uterus, fallopian tubes, and vagin With other hormones, such as pituitary hormones and pr gesterone, they cause enlargement of the breasts throug promotion of ductal growth, stromal development, and th accretion of fat. Estrogens are intricately involved wit other hormones, especially progesterone, in the processes the ovulatory menstrual cycle and pregnancy, and affect th release of pituitary gonadotropins. They also contribute the shaping of the skeleton, maintenance of tone and ela ticity of urogenital structures, changes in the epiphyses the long bones that allow for the pubertal growth spurt an its termination, and pigmentation of the nipples and gen tals.

Estrogens occur naturally in several forms. The primar source of estrogen in normally cycling adult women is th ovarian follicle, which secretes 70 to 500 micrograms of es tradiol daily, depending on the phase of the menstrual cycl This is converted primarily to estrone, which circulates i roughly equal proportion to estradiol, and to small amount of estriol. After menopause, most endogenous estrogen i produced by conversion of androstenedione, secreted by th adrenal cortex, to estrone by peripheral tissues. Thus, es trone—especially in its sulfate ester form—is the mos abundant circulating estrogen in postmenopausal women Although circulating estrogens exist in a dynamic equilib rium of metabolic interconversions, estradiol is the princi pal intracellular human estrogen and is substantially mor potent than estrone or estriol at the receptor.

Information Regarding Lipid Effects

The results of a clinical trial conducted in a 97% Caucasia population at low risk for cardiovascular disease show tha Premarin significantly increases HDL-C and the HDL_2 subfraction and significantly decreases LDL-C.

The following table summarizes mean percent changes fro baseline lipid parameter values after 1 year of treatmer with Premarin.

MEAN PERCENT CHANGE FROM BASELINE LIPID PROFILE VALUES AFTER ONE YEAR OF TREATMEN

Lipid Parameter	Premarin 0.625 mg Dose
Total Cholesterol	0.2
HDL-C	14.1*
HDL_2-C	70.8*
LDL-C	-7.7*
Triglycerides	39.4*

* Significantly ($p \leq 0.05$) different from baseline value.

PHARMACOKINETICS

Absorption

Conjugated estrogens used in therapy are soluble in wat and are well absorbed from the gastrointestinal tract afb release from the drug formulation. Maximum plasma co centrations of the various conjugated and unconjugated e trogens are attained within 4 to 10 hours after oral admi istration.

Estrogens used in therapy are also well absorbed throu the skin and mucous membranes. When applied for a loc action, absorption is usually sufficient to cause systemic fects. When conjugated with aryl and alkyl groups for pe enteral administration, the rate of absorption of oily prep rations is slowed with a prolonged duration of action, su that a single intramuscular injection of estradiol valerate estradiol cypionate is absorbed over several weeks.

Distribution

Although naturally-occurring estrogens circulate in t blood largely bound to sex hormone-binding globul (SHBG) and albumin, only unbound estrogens enter targ tissue cells. (Conjugated estrogens bind mainly to albumi unconjugated estrogens bind to both albumin and SHB The apparent terminal-phase disposition half-life ($t_{1/2}$) the various estrogens is prolonged by the slow absorpti from Premarin and ranges from 10 to 24 hours.

Metabolism

Administered estrogens and their esters are handled with the body essentially the same as the endogenous hormon Metabolic conversion of estrogens occurs primarily in t liver (first-pass effect), but also at local target tissue sit Complex metabolic processes result in a dynamic equil rium of circulating conjugated and unconjugated estroge forms which are continually interconverted, especially b tween estrone and estradiol and between esterified and n esterified forms. A significant proportion of the circulati estrogen exists as sulfate conjugates, especially estrone s fate, which serves as a circulating reservoir for the form tion of more active estrogenic species. A certain proporti of the estrogen is excreted into the bile, then reabsort from the intestine and returned to the liver through the p tal venous system. During this enterohepatic recirculati estrogens are desulfated and resulfated and undergo deg dation through conversion to less active estrogens (esti and other estrogens), oxidation to nonestrogenic substan (catecholestrogens, which interact with catecholamine n tabolism, especially in the central nervous system), and c jugation with glucuronic acids (which are then rapidly creted in the urine).

When given orally, naturally-occurring estrogens and th esters are extensively metabolized (first-pass effect) and culate primarily as estrone sulfate, with smaller amount other conjugated and unconjugated estrogenic species. T results in limited oral potency. By contrast, synthetic es

uch as ethinyl estradiol and the nonsteroidal estro-
re degraded very slowly in the liver and other tis-
hich results in their high intrinsic potency. Estrogen
roducts administered by non-oral routes are not sub-
first-pass metabolism, but also undergo significant
: uptake, metabolism, and enterohepatic recycling.
ion
soluble estrogen conjugates are strongly acidic and
ized in body fluids, which favor excretion through the
s since tubular reabsorption is minimal.
ible 1 at right)

CATIONS AND USAGE

en drug products are indicated in the:
atment of moderate to severe vasomotor symptoms as-
d with the menopause. There is no adequate evidence
strogens are effective for nervous symptoms or depres-
hich might occur during menopause and they should
used to treat these conditions.
atment of vulvar and vaginal atrophy.
atment of hypoestrogenism due to hypogonadism, cas-
n or primary ovarian failure.
atment of breast cancer (for palliation only) in appro-
ly selected women and men with metastatic disease.
atment of advanced androgen-dependent carcinoma of
rostate (for palliation only).
vention of osteoporosis. Since estrogen administration
ociated with risk, selection of patients ideally should
sed on prospective identification of risk factors for de-
ing osteoporosis. Unfortunately, there is no certain
o identify those women who will develop osteoporotic
ures. Most prospective studies of efficacy for this indi-
have been carried out in white menopausal women,
ut stratification by other risk factors, and tend to show
versally salutary effect on bone. Thus, patient selection
be individualized based on the balance of risks and
its. A more favorable risk/benefit ratio exists in a hys-
omized woman because she has no risk of endometrial
r (see Boxed Warning).
gen replacement therapy reduces bone resorption and
ls or halts postmenopausal bone loss. Case-control
es have shown an approximately 60 percent reduction
and wrist fractures in women whose estrogen replace-
was begun within a few years of menopause. Studies
uggest that estrogen reduces the rate of vertebral frac-
Even when started as late as 6 years after meno-
estrogen prevents further loss of bone mass for as
s the treatment is continued. When estrogen therapy
continued, bone mass declines at a rate comparable to
mediate postmenopausal period. There is no evidence
estrogen replacement therapy restores bone mass to
enopausal levels.
eletal maturity there are sex and race differences in
the total amount of bone present and its density, in
of men and blacks. Thus, women are at higher risk
men because they start with less bone mass and, for
al years following natural or induced menopause, the
f bone mass decline is accelerated. White and Asian
n are at higher risk than black women.
menopause is one of the strongest predictors for the
opment of osteoporosis. In addition, other factors af-
g the skeleton which are associated with osteoporosis
le genetic factors (small build, family history), endo-
factors (nulliparity, thyrotoxicosis, hyperparathyroid-
Cushing's syndrome, hyperprolactinemia, Type I diabe-
lifestyle (cigarette smoking, alcohol abuse, sedentary
ise habits), and nutrition (below average body weight,
y calcium intake).
mainstays of prevention and management of osteoporo-
e estrogen, an adequate lifetime calcium intake, and
ise. Postmenopausal women absorb dietary calcium
fficiently than premenopausal women and require an
ge of 1500 mg/day of elemental calcium to remain in
al calcium balance. By comparison, premenopausal
n require about 1,000 mg/day and the average calcium
in the USA is 400–600 mg/day. Therefore, when not
indicated, calcium supplementation may be helpful.
t-bearing exercise and nutrition may be important
cts to the prevention and management of osteoporosis.
bilization and prolonged bed rest produce rapid bone
while weight-bearing exercise has been shown both to
e bone loss and to increase bone mass. The optimal
nd amount of physical activity that would prevent os-
rosis have not been established, however in two stud-
hour of walking and running exercises twice or three
weekly significantly increased lumbar spine bone

TRAINDICATIONS

gens should not be used in individuals with any of the
ing conditions:
own or suspected pregnancy (see Boxed Warning).
gen may cause fetal harm when administered to a
ant woman.
diagnosed abnormal genital bleeding.
own or suspected cancer of the breast except in appro-
ly selected patients being treated for metastatic dis-

own or suspected estrogen-dependent neoplasia.
tive thrombophlebitis or thromboembolic disorders.
is insufficient information regarding women who
had previous thromboembolic disease.
marin Tablets should not be used in patients hyper-

TABLE 1. PHARMACOKINETIC PARAMETERS FOR PREMARIN
Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg

Drug	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
estrone	139	8.8	28.0	5016
baseline-adjusted estrone	120	8.8	17.4	2956
equilin	66	7.9	13.6	1210

Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 2 x 0.625 mg

Drug	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
total estrone	7.3	7.3	15.0	134
baseline-adjusted total estrone	7.1	7.3	13.6	122
total equilin	5.0	6.2	10.1	65

WARNINGS

1. *Induction of malignant neoplasms.*
Breast cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some studies have reported a moderately increased risk (relative risks of 1.3 to 2.0) in those women taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.
In the three year clinical Postmenopausal Estrogen Progestin Intervention (PEPI) trial of 875 women to assess differences among placebo, unopposed Premarin, and three different combination hormone therapy regimens, one (1) new case of breast cancer was detected in the placebo group (n=174), one in the Premarin alone group (n=175), none in the continuous Premarin plus continuous medroxyprogesterone acetate group (n=174), and two (2) in the continuous Premarin plus cyclic medroxyprogesterone acetate group (n=174).
Women on this therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 50 should have regular mammograms.
Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see **PRECAUTIONS**).
Congenital lesions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.
2. *Gallbladder disease.* Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.
3. *Thromboembolic disorders and other vascular problems.* In some studies, women on estrogen replacement therapy, given alone or in combination with a progestin, have been reported to have an increased risk of thrombophlebitis, and/or thromboembolic disease. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis; cerebral embolism, and pulmonary embolism) during estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.
4. *Elevated blood pressure.* Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.
5. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

A. General
1. *Addition of a progestin.* Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of any hyperplastic changes.
There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. The potential risks include adverse effects on lipoprotein metabolism, impairment of glucose tolerance, and possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see **PRECAUTIONS** below).
The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.
2. *Cardiovascular risk.* A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.
In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy *without added progestins* and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:
(1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.
(2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see **PRECAUTIONS** and **WARNINGS**). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL cholesterol levels.
(3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see **WARNINGS**).
Because relatively long-term use of estrogens by a woman with a uterus has been shown to increase the risk of endometrial cancer, physicians often recommend that these women should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, clinical trials and future epidemiological studies are required to clarify these issues.
3. *Physical examination.* A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.
4. *Hypercoagulability.* Some studies have shown that women taking estrogen replacement therapy have hyperco-

Continued on next page

Premarin Tablets—Cont.

agulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

5. *Familial hyperlipoproteinemia.* Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

6. *Fluid retention.* Because estrogens may cause some degree of fluid retention, conditions which might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

7. *Uterine bleeding and mastodynia.* Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

8. *Impaired liver function.* Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

9. *Uterine fibroids.* Pre-existing uterine leiomyomata may increase in size during estrogen use.

10. *Hypocalcemia.* Estrogens should be used with caution in individuals with metabolic bone disease associated with severe hypocalcemia.

B. **Information for the Patient.** See text of Patient Package Insert which appears after the **HOW SUPPLIED** section.

C. **Laboratory Tests.**

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention of osteoporosis, however, see **DOSAGE AND ADMINISTRATION** section.

D. **Drug/Laboratory Test Interactions.**

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

E. **Carcinogenesis, Mutagenesis, and Impairment of Fertility.** Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. See **CONTRAINDICATIONS** and **WARNINGS**.

F. **Pregnancy Category X.** Estrogens should not be used during pregnancy. See **CONTRAINDICATIONS** and Boxed Warning.

G. **Nursing Mothers.**

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

H. **Pediatric Use.** See **DOSAGE AND ADMINISTRATION.**

ADVERSE REACTIONS

The following additional adverse reactions have been reported with estrogen therapy (see **WARNINGS** regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia; see **PRECAUTIONS** regarding cardiovascular risk).

1. Genito-urinary system.
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting.
Increase in size of uterine leiomyomata.
Vaginal candidiasis.
Change in amount of cervical secretion.

2. Breasts.
Tenderness, enlargement.

3. Gastrointestinal.
Nausea, vomiting.
Abdominal cramps, bloating.
Cholestatic jaundice.
Increased incidence of gallbladder disease.
Pancreatitis.

4. Skin.
Chloasma or melasma that may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.

5. Cardiovascular.
Venous thromboembolism.
Pulmonary embolism.

6. Eyes.
Steepening of corneal curvature.
Intolerance to contact lenses.

7. Central Nervous System.
Headache.
Migraine.
Dizziness.
Mental depression.
Chorea.

8. Miscellaneous.
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

1. For treatment of moderate to severe vasomotor symptoms, and/or vulvar and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Vasomotor symptoms—0.625 mg daily.
Vulvar and vaginal atrophy—0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient.
Premarin® therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized basis.
Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

2. For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:
Female hypogonadism—0.3 mg to 0.625 mg daily, administered cyclically (e.g., three weeks on and one week off). Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium.
In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 0.15 mg. The dosage may be gradually titrated upward at 6 to 12 month intervals as needed to achieve appropriate bone age advancement and eventual epiphyseal closure. Clinical studies suggest that doses of 0.15 mg, 0.3 mg, and 0.6 mg are associated with mean ratios of bone age advancement to chronological age progression ΔBA/ΔCA) of 1.1, 1.5, and 2.1, respectively. (Premarin in the dose strength of 0.15 mg is not available commercially). Available data suggest that chronic dosing with 0.625 mg is sufficient to induce artificial cyclic menses with sequential progestin treatment and to maintain bone mineral density after skeletal maturity is achieved.
Female castration or primary ovarian failure—1.25 mg daily, cyclically. Adjust dosage, upward or downward, according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

3. For treatment of breast cancer, for palliation only, in appropriately selected women and men with metastatic disease:
Suggested dosage is 10 mg three times daily for a period of at least three months.

4. For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only:
1.25 mg to 2.5 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

5. For prevention of osteoporosis:
0.625 mg daily. Premarin therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized basis.

HOW SUPPLIED

Premarin® (conjugated estrogens tablets, USP)
— Each oval purple tablet contains 2.5 mg, in bottles of 100 (NDC 0046-0865-81) and 1,000 (NDC 0046-0865-91).
— Each oval yellow tablet contains 1.25 mg, in bottles of 100 (NDC 0046-0866-81); 1,000 (NDC 0046-0866-91); 5,000 (NDC 0046-0866-95); and Unit-Dose packages of 100 (NDC 0046-0866-99).
— Each oval white tablet contains 0.9 mg, in bottles of 1((NDC 0046-0864-81).
— Each oval maroon tablet contains 0.625 mg, in bottles 100 (NDC 0046-0867-81); 1,000 (NDC 0046-0867-91 5,000 (NDC 0046-0867-95); and Unit-Dose packages 100 (NDC 0046-0867-99).
— Each oval green tablet contains 0.3 mg, in bottles of 1((NDC 0046-0868-81) and 1,000 (NDC 0046-0868-91).
The appearance of these tablets is a trademark of Wyet Ayerst Laboratories.
Store at room temperature (approximately 25° C).
Dispense in a well-closed container as defined in the US

INTRODUCTION

This leaflet describes when and how to use estrogens ar the risks of estrogen treatment.
Estrogens have important benefits but also some risks. Y must decide, with your doctor, whether the risks to you estrogen use are acceptable because of their benefits. If y decide to start taking estrogens, check with your doctor make sure you are using the lowest possible effective dos and that you use them for only as long as necessary. Ho long you need to use estrogens will depend upon the reaso for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").
If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual change of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

USES OF ESTROGEN

(Not every estrogen drug is approved for every use listed i this section. If you want to know which of these possibl uses are approved for the medicine prescribed for you, as your doctor or pharmacist to show you the professional la beling. You can also look up the specific estrogen product i a book called *The Physicians' Desk Reference,* which is avail able in many book stores and public libraries. Generic drug carry virtually the same labeling information as their bran name versions.)

To reduce moderate to severe menopausal symptoms.
Estrogens are hormones made by the ovaries of norma women. Between ages 45 and 55, the ovaries normally sto making estrogens. This leads to a drop in body estrogen le els which causes the "change of life" or menopause (the en of monthly menstrual periods). If both ovaries are remove during an operation before natural menopause takes plac the sudden drop in estrogen levels causes "surgical meno pause."
When the estrogen levels begin dropping, some women de velop very uncomfortable symptoms, such as feeling o warmth in the face, neck, and chest, or sudden intense epi sodes of heat and sweating ("hot flashes" or "hot flushes". Using estrogen drugs can help the body adjust to lower es trogen levels and reduce these symptoms. In some women the symptoms are mild; in others they can be severe. Thes symptoms may last only a few months or longer. Takin Premarin can alleviate these symptoms. If you are not tak ing estrogen for other reasons, such as the prevention of os teoporosis, you should take Premarin only as long as yo need it for relief from your menopausal symptoms.
To treat vulvar and vaginal atrophy (itching, burning, dry ness in or around the vagina, difficulty or burning on urina tion) associated with menopause.
To treat certain conditions in which a young woman's ova ries do not produce enough estrogen naturally.
To treat certain types of abnormal uterine bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.
To treat certain cancers in special situations, in men and women.
To prevent thinning of bones.
Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to

osteoporosis. Regular weight-bearing exercise (like
; and running for an hour, two or three times a week)
so help to prevent osteoporosis. Before you change
cium intake or exercise habits, it is important to dis-
ese lifestyle changes with your doctor to find out if
e safe for you. Since estrogen use has some risks,
omen who are likely to develop osteoporosis should
ogens for prevention. Women who are likely to de-
teoporosis often have the following characteristics:
r Asian race, slim, cigarette smokers, and a family
of osteoporosis in a mother, sister, or aunt. Women
ve relatively early menopause, often because their
were removed during an operation ("surgical meno-
. are more likely to develop osteoporosis than women
enopause happens at the average age.

HOULD NOT USE ESTROGENS

os should not be used:

pregnancy (see Boxed Warning).

hink you may be pregnant, do not use any form of
-containing drug. Using estrogens while you are
it may cause your unborn child to have birth defects.
os do not prevent miscarriage.

ave unusual vaginal bleeding which has not been
d by your doctor (see Boxed Warning).

l vaginal bleeding can be a warning sign of cancer of
us, especially if it happens after menopause. Your
ust find out the cause of the bleeding so that he or
recommend the proper treatment. Taking estrogens
visiting your doctor can cause you serious harm if
ginal bleeding is caused by cancer of the uterus.

ve had cancer.

trogens increase the risk of certain types of cancer,
ld not use estrogens if you have ever had cancer of
st or uterus, unless your doctor recommends that
may help in the cancer treatment. (For certain pa-
ith breast or prostate cancer, estrogens may help.)

ve any circulation problems.

drugs should not be used except in unusually spe-
ations in which your doctor judges that you need
therapy so much that the risks are acceptable.
l women with abnormal blood clotting conditions
void estrogen use (see **RISKS OF ESTROGENS**, be-

y do not work.

nenopause, some women develop nervous symp-
depression. Estrogens do not relieve these symp-
t may have heard that taking estrogens for years
opause will keep your skin soft and supple and
feeling young. There is no evidence for these
d such long-term estrogen use may have serious

dbirth or when breastfeeding a baby.

should not be used to try to stop the breasts from
h milk after a baby is born. Such treatment may
he risk of developing blood clots (see **RISKS OF ES-**
, below).

breastfeeding, you should avoid using any drugs
any drugs pass through to the baby in the milk.
sing a baby, you should take drugs only on the
our health-care provider.

ESTROGENS

the uterus.

f developing cancer of the uterus gets higher the
use estrogens and the larger doses you use. One
ed that after women stop taking estrogens, this
cer risk quickly returns to the usual level of risk
had never used estrogen therapy). Three other
owed that the cancer risk stayed high for 8 to
15 years after stopping estrogen treatment. Be-
is risk, **IT IS IMPORTANT TO TAKE THE LOWEST**
T WORKS AND TO TAKE IT ONLY AS LONG AS
IT.

estin therapy together with estrogen therapy
the higher risk of uterine cancer related to es-
(but see **OTHER INFORMATION**, below).

had your uterus removed (total hysterectomy),
risk of developing cancer of the uterus.

e breast.

s have not shown a higher risk of breast cancer
who have ever used estrogens. However, some
reported that breast cancer developed more of-
wice the usual rate) in women who used estro-
ng periods of time (especially more than 10
ho used higher doses for shorter time periods.
ast examinations by a health professional and
f-examination are recommended for women re-
gen therapy, as they are for all women. Regular
ns are recommended for all women over
ge.

disease.

use estrogens after menopause are more likely
llbladder disease needing surgery than women
se estrogens.

of the pancreas (Pancreatitis).

high triglyceride levels may have an increased
ping inflammation of the pancreas.

od clotting.

gens may cause changes in your blood clotting
e changes allow the blood to clot more easily,
ing clots to form in your bloodstream. If blood
in your bloodstream, they can cut off the blood
al organs, causing serious problems. These
y include a stroke (by cutting off blood to the
rt attack (by cutting off blood to the heart), a
nbolus (by cutting off blood to the lungs), or
other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

Nausea and vomiting.

Breast tenderness or enlargement.

Enlargement of benign tumors ("fibroids") of the uterus.

Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

See your doctor regularly.

While you are using estrogens, it is important to visit your doctor at least once a year for a checkup. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

Reassess your need for estrogens.

You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble.

If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine cancer)
- Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
- Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)
- Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)
- Yellowing of the skin or eyes (possible liver problem)
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormonal drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

You should know, however, that taking estrogens *with* progestins may have additional risks. These may include unhealthy effects on blood fats (especially the lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease). However, while it has been reported that some estrogen and progestin combinations have an unfavorable effect on blood fats, studies of Premarin given with medroxyprogesterone acetate (MPA) (0.625 mg Premarin with either 2.5 mg MPA continuously or 5 mg of MPA cyclically) have shown decreases in LDL ("bad" cholesterol) and increases in HDL ("good" cholesterol). Other risks include unhealthy effects on blood sugars, which might make a diabetic condition worse, and a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken *without* progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health-care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about the amounts recommended.

4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

5. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called *The Physicians' Desk Reference*, which is available in bookstores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

HOW SUPPLIED

Premarin® (conjugated estrogens tablets, USP)—tablets for oral administration.

Each oval purple tablet contains 2.5 mg.

Each oval yellow tablet contains 1.25 mg.

Each oval white tablet contains 0.9 mg.

Each oval maroon tablet contains 0.625 mg.

Each oval green tablet contains 0.3 mg.

The appearance of these tablets is a trademark of Wyeth-Ayerst Laboratories.

Manufactured by:
Ayerst Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

Shown in Product Identification Guide, page 343

PREMARIN® R

[prĕm 'a-rin]

(conjugated estrogens)

VAGINAL CREAM

in a nonliquefying base

Rx only

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent, case-controlled studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year.[1–3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer-reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case-controlled studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed, on at least a semiannual basis, to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration.[3] It therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing, in later life, a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1,000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30% to 90%) have been found to have vaginal adenosis,[8–12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13–16] One case-controlled study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than 1 per 1,000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses.

If Premarin (conjugated estrogens) Vaginal Cream is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION

Each gram of Premarin® (conjugated estrogens) Vaginal Cream contains 0.625 mg conjugated estrogens, USP in a

Continued on next page

Premarin Vaginal Cream—Co

Premarin Vaginal Cream exposure has been reported to weaken latex condoms. The potential for Premarin Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

HOW SUPPLIED

Premarin® (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP.

Combination package: Each contains Net Wt. 1 1/2 oz (42.5 g) tube with one plastic applicator calibrated in 1/2 g increments to a maximum of 2 g (NDC 0046-0872-93).

Also Available —Refill package: Each contains Net Wt. 1 1/2 oz (42.5 g) tube (NDC 0046-0872-01).

Store at room temperature (approximately 25° C).

INSTRUCTIONS FOR USE OF PREMARIN®
(conjugated estrogens)

Vaginal Cream Gentle Measure™ Applicator:

The Gentle Measure Applicator has been specifically designed for comfortable, easy use.

1. Remove cap from tube.
2. Screw nozzle end of applicator onto tube.
3. *Gently* squeeze tube from the *bottom* to force sufficient cream into the barrel to provide the prescribed dose. Use the marked stopping points on the applicator as a guideline to measure the correct dose.
4. Unscrew applicator from tube.
5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.

TO CLEANSE: Pull plunger to remove it from barrel. Wash with mild soap and warm water.

DO NOT BOIL OR USE HOT WATER.

Manufactured by:
Ayerst Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

Shown in Product Identification Guide, page 343

PREMPRO™ ℞
(conjugated estrogens/medroxyprogesterone acetate tablets)

PREMPHASE®
(conjugated estrogens/medroxyprogesterone acetate tablets)

Caution: Federal law prohibits dispensing without prescription.

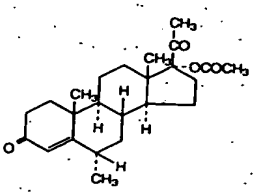
DESCRIPTION

PREMPRO therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin® tablets and 2.5 mg or 5 mg of medroxyprogesterone acetate (MPA) for oral administration.

PREMPHASE therapy consists of two separate tablets, a maroon Premarin tablet containing 0.625 mg of conjugated estrogens which is taken orally on days 1 through 14 and a light-blue tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate (MPA) which is taken orally on days 15 through 28.

The conjugated estrogens found in Premarin tablets are a mixture of sodium estrone sulfate and sodium equilin sulfate. They contain as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol and 17β-dihydroequilin.

Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless, crystalline powder, stable in air, melting between 200° C and 210° C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for MPA is pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. Its molecular formula is $C_{24}H_{34}O_4$, with a molecular weight of 386.53. Its structural formula is:



PREMPRO 2.5 mg

Each peach tablet for oral administration contains 0.625 mg conjugated estrogens, 2.5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and red ferric oxide.

PREMPRO 5.0 mg

Each light-blue tablet for oral administration contains 0.625 mg conjugated estrogens, 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No. 2.

PREMPHASE

Each maroon Premarin tablet for oral administration contains 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Red No. 27, FD&C Red No. 40. These tablets comply with USP Drug Release Test 1.

Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C Blue No.2.

CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 pg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by interconversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheal tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

The pharmacologic effects of the administered conjugated estrogens are similar to those of endogenous estrogens. In responsive tissue (female genital organs, breasts, hypothalamus, pituitary) estrogens enter the cell and are transported into the nucleus. As a result of the estrogen action, specific RNA and protein synthesis occurs.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The results of clinical studies indicate that the addition of a progestin to an estrogen replacement regimen for more than 10 days per cycle reduces the incidence of endometrial hyperplasia and the attendant risk of adenocarcinoma in women with intact uteri. The addition of a progestin to an estrogen replacement regimen has not been shown to interfere with the efficacy of estrogen replacement therapy for its approved indications.

Androgenic and anabolic effects of medroxyprogesterone acetate (MPA) have been noted, but the drug is apparently devoid of significant estrogenic activity. Parenterally administered MPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, although available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses. MPA may achieve its beneficial effect on the endometrium in part by decreasing nuclear estradiol receptors and suppression of epithelial DNA synthesis in endometrial tissue.

PHARMACOKINETICS

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. However, PREMPRO and PREMPHASE contain a formulation of MPA that is immediately released and a modified-release formulation of conjugated estrogens that slowly releases estrogens over several hours. Maximum plasma concentrations of the various conjugated and unconjugated estrogens are attained within 4 to 10 hours after dose administration. MPA is well absorbed from the gastrointestinal tract, and maximum MPA plasma concentrations are attained within 2 to 4 hours after dose administration. Table 1 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens, and medroxyprogesterone acetate following administration of 0.625 mg/2.5 mg and 0.625 mg/5mg tablets to healthy postmenopausal women.

Food-Effect: Single dose studies in healthy, postmenopausal women were conducted to investigate any potential drug interaction when PREMPRO or PREMPHASE is administered with a high fat breakfast. Administration with food decreased the C_{max} of total estrone by 18 to 34% and increased total equilin C_{max} by 38% compared to the fast state, with no other effect on the rate or extent of absorpt of other conjugated or unconjugated estrogens. Administ tion with food approximately doubles MPA C_{max} and creases MPA AUC by approximately 20 to 30%.

Dose Proportionality: The C_{max} and AUC values for M observed in two separate pharmacokinetic studies c ducted with PREMPRO or PREMPHASE 2 × 0.625 mg/ mg and 2 × 0.625 mg/5mg tablets exhibited nonlinear dc proportionality; doubling the MPA dose from 2 × 2.5 to 2 5.0 mg increased the mean C_{max} and AUC by 3.2 and folds, respectively. The apparent clearance (Cl/F) of MPA o tained with 2 × 0.625 mg/5 mg tablets was lower than th observed with 2 × 0.625 mg/2.5 mg tablets.

[See table 1 at top of next page]

Distribution

The conjugated estrogens bind mainly to albumin, but th unconjugated estrogens bind to both albumin and sex-ho mone-binding globulin (SHBG). MPA is approximately 90 bound to plasma proteins but does not bind to SHBG.

Metabolism

Metabolism and inactivation of estrogens occur primarily i the liver. Some estrogens are excreted into the bile; hov ever, they are reabsorbed from the intestine and returned t the liver through the portal venous system. Metabolism an elimination of MPA occurs primarily in the liver via hydro ylation, with subsequent conjugation and elimination in th urine.

Excretion

Water-soluble estrogen conjugates are strongly acidic an are ionized in body fluids, which favor excretion through th kidneys since tubular reabsorption is minimal. The appai ent terminal-phase disposition half-life ($t_{1/2}$) of the variou estrogens is prolonged by the slow absorption from PREM PRO and PREMPHASE and ranges from 10 to 24 hour Most metabolites of MPA are excreted as glucuronide conjt gates with only minor amounts excreted as sulfates. MP has a $t_{1/2}$ ranging from 38 to 46 hours.

Drug-Interactions

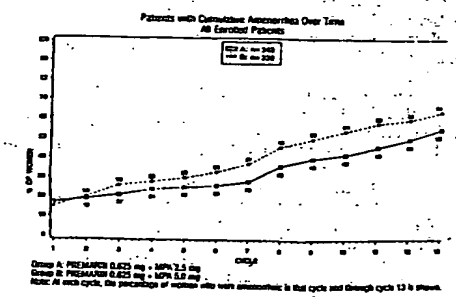
Coadministration of conjugated estrogens with MPA doe not affect the pharmacokinetic profile of MPA. Similarly MPA does not affect the pharmacokinetic profile of the con jugated or unconjugated estrogens.

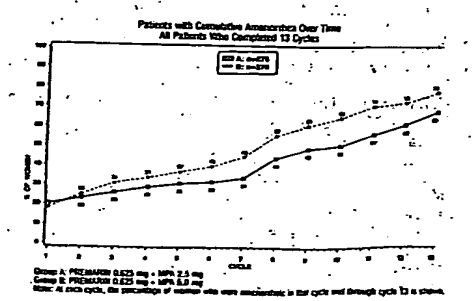
CLINICAL STUDIES

In a 1-year clinical trial of 1376 women randomized t PREMPRO 0.625 mg/2.5 mg (Regimen A, n=340), PREM PRO 0.625 mg/5 mg (Regimen B, n=338), PREMPHASI 0.625 mg/5 mg (Regimen C, n=351), or Premarin 0.625 m alone (n=347), results of evaluable biopsies at 12 month (n=279 for Regimen A, 274 for Regimen B, 277 for Regimen C, and 283 for Premarin alone) showed a reduced risk o endometrial hyperplasia in the two PREMPRO treatmen groups (less than 1%) and in the PREMPHASE treatmen group (less than 1%; 1% when focal hyperplasia was in cluded) compared to the Premarin group (8%; 20% when fo cal hyperplasia was included). See Table 2.

[See table 2 at bottom of next page]

In this clinical trial the incidence of amenorrhea increase over time in both PREMPRO groups. Seventeen percent o the patients randomized to Regimen A experienced amenor rhea during the entire 13 cycles of the study, and 15 percen of the patients on Regimen B experienced amenorrhea dur ing the entire 13 cycles of the study. The following two fig ures describe cumulative amenorrhea which is defined a amenorrhea continuing from a given cycle to the end of th study.





Information Regarding Lipid Effects

The results of a clinical trial conducted in a 97% Caucasiar population at low risk for cardiovascular disease, showec that the increases in HDL-C and HDL_2-C subfraction were

Table 1. PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS (CE), AND MEDROXYPROGESTERONE ACETATE

UG	2 × 0.625 mg CE/2.5 mg MPA Combination Tablets (n=54)				2 × 0.625 mg CE/5 mg MPA Combination Tablets (n=51)			
PK Parameter Geometric Mean (SD)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)	C_{max} (pg/mL)	t_{max} (h)	(h)	AUC (pg•h/mL)
conjugated Estrogens								
rone	175 (41)	7.6 (1.8)	31.6 (7.4)	5358 (1840)	124 (53)	10 (3.5)	62.2 (85.2)	6303 (2542)
*-Estrone	159 (41)	7.6 (1.8)	16.9 (5.8)	3313 (1310)	104 (51)	10 (3.5)	26.0 (25.9)	3136 (1598)
ıilin	71 (22)	5.8 (2.0)	9.9 (3.5)	951 (413)	52 (23)	8.9 (3.0)	15.5 (8.2)	1179 (540)
PK Parameter Geometric Mean (SD)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
njugated Estrogens								
al Estrone	6.6 (2.5)	6.1 (1.7)	20.7 (7.0)	116 (68)	6.3 (3.0)	9.1 (2.6)	23.6 (8.4)	151 (63)
*-Total Estrone	6.4 (2.5)	6.1 (1.7)	15.4 (5.2)	100 (57)	6.2 (3.0)	9.1 (2.6)	20.6 (7.3)	139 (56)
al Equilin	5.1 (2.3)	4.6 (1.6)	11.4 (2.9)	50 (35)	4.2 (2.2)	7.0 (2.5)	17.2 (22.6)	72 (36)
droxyprogesterone state	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	Cl/F (L/h/kg)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	Cl/F (L/h/kg)
PA	1.5 (0.6)	2.8 (1.5)	37.6 (11.2)	2.3 (0.7)	48 (1.5)	2.4 (1.2)	46.3 (18.0)	1.6 (0.5)

* = Baseline Adjusted
ax = peak plasma concentration
x = time peak concentration occurs
= terminal-phase disposition half-life ($0.693/\lambda_z$)
C = total area under the curve
F = apparent oral clearance

nificantly less for PREMPRO and PREMPHASE than marin alone, but decreases in LDL-C were comparable h Premarin alone. Compared with Premarin, total Choerol concentrations were significantly lower after 1 year reatment than at baseline among patients receiving EMPRO or PREMPHASE.

following table summarizes mean percent changes from eline lipid parameter values after 1 year of treatment the combined regimens.

table 3 at top of next page]

DICATIONS AND USAGE

EMPRO or PREMPHASE therapy is indicated in women an intact uterus for the:

reatment of moderate to severe vasomotor symptoms asted with the menopause. There is no adequate evidence estrogens are effective for nervous symptoms or depreswhich might occur during menopause and they should be used to treat these conditions.

reatment of vulvar and vaginal atrophy.

revention of osteoporosis.

e estrogen administration is associated with risks as as benefits, selection of patients ideally should be based rospective identification of risk factors for developing porosis. Unfortunately, there is no certain way to identhose women who will develop osteoporotic fractures. prospective studies of efficacy for this indication have carried out in white menopausal women, without ification by other risk factors, and tend to show a unilly salutary effect on bone. Thus, patient selection be individualized based on the balance of risks and its.

gen replacement therapy reduces bone resorption and ds or halts postmenopausal bone loss. Case-control es have shown an approximately 60% reduction in hip rist fractures in women whose estrogen replacement egun within a few years of menopause. Studies also st that estrogen reduces the rate of vertebral fracEven when started as late as 6 years after meno, estrogen may prevent further loss of bone mass for g as the treatment is continued. When estrogen therdiscontinued, bone mass declines at a rate comparathat in the immediate postmenopausal period. There evidence that estrogen replacement therapy restores nass to premenopausal levels.

iletal maturity there are sex and race differences in he total amount of bone present and its density, in of men and blacks. Thus, women are at higher risk nen because they start with less bone mass and, for l years following natural or induced menopause, the bone mass decline is accelerated. White and Asian are at higher risk than black women.

menopause is one of the strongest predictors for the ment of osteoporosis. In addition, other factors afthe skeleton which are associated with osteoporosis genetic factors (small build, family history), endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1000 mg/day and the average calcium intake in the USA is 400–600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established; however, in two studies an hour of walking and running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women under any of the following conditions or circumstances:

1. Known or suspected pregnancy, including use for missed abortion or as a diagnostic test for pregnancy. Estrogen or progestin may cause fetal harm when administered to a pregnant woman.
2. Known or suspected cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Undiagnosed abnormal genital bleeding.
5. Active or past history of thrombophlebitis, thromboembolic disorders, or stroke.
6. Liver dysfunction or disease.

PREMPRO or PREMPHASE therapy should not be used in patients hypersensitive to the ingredients contained in the tablets.

WARNINGS

ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT.

Based on experience with estrogens and/or progestins:

1. *Induction of malignant neoplasms*

Endometrial cancer. The reported endometrial cancer risk among users of unopposed estrogen was about 2- to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. There is no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal.

A large clinical trial has demonstrated that when MPA is administered with Premarin, there is a markedly reduced incidence of endometrial hyperplasia, a possible precursor of endometrial cancer. Endometrial hyperplasia has been reported in a large clinical trial to occur at a rate of approximately 1% or less with PREMPRO AND PREMPHASE. Studies have also demonstrated a reduced risk of endometrial cancer when a progestin is administered with estrogen replacement therapy. In the large clinical trial described above, only a single case of endometrial cancer was reported to occur among women taking combination Premarin/MPA therapy.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equivalent estrogen doses.

Breast cancer. Some studies have reported a moderately increased risk of breast cancer (relative risk of 1.3 to 2.0) in those women on estrogen replacement therapy taking higher doses, or in those taking lower doses for prolonged periods of time, especially in excess of 10 years. The majority of studies, however, have not shown an association in women who have ever used estrogen replacement therapy.

The effect of added progestins on the risk of breast cancer is unknown, although a moderately increased risk in those taking combination estrogen/progestin therapy has been reported. Other studies have not shown this relationship. In a one year clinical trial of PREMPRO, PREMPHASE and Premarin alone, 5 new cases of breast cancer were detected among 1377 women who received the combination treatments, while no new cases were detected among 347 women who received Premarin alone. The overall incidence of breast cancer in this clinical trial does not exceed that expected in the general population. In the three year clinical Postmenopausal Estrogen Progestin Intervention (PEPI) trial of 875 women to assess differences among placebo, unopposed Premarin, and three different combination hormone therapy regimens, one (1) new case of breast cancer was detected in the placebo group (n=174), one in the Premarin alone group (n=175), none in the continuous Premarin plus continuous medroxyprogesterone acetate group (n=174), and two (2) in the continuous Premarin plus cyclic medroxyprogesterone acetate group (n=174).

Women on hormone replacement therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 50 should have regular mammograms.

2. *Thromboembolic Disorders and Other Vascular Problems.*

In some studies, women on estrogen replacement therapy, given alone or in combination with a progestin, have been reported to have an increased risk of thrombophlebitis, and/or thromboembolic disease. The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during hormone replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, hormone replacement therapy should be discontinued immediately. Women who have risk factors for thrombotic disorders should be kept under careful observation.

Table 2. INCIDENCE OF ENDOMETRIAL HYPERPLASIA AFTER ONE YEAR OF TREATMENT

	Groups			
	PREMPRO 0.625 mg/2.5 mg	PREMPRO 0.625 mg/5 mg	PREMPHASE 0.625 mg/5 mg	Premarin 0.625 mg
mber of patients	340	338	351	347
: of patients with le biopsies	279	274	277	283
of patients with biopsies				
al and non-focal hyperplasia	2 (<1)*	0 (0)*	3 (1)*	57 (20)
ling focal cystic hyperplasia	2 (<1)*	0 (0)*	1 (<1)*	25 (8)

ant ($p < 0.001$) in comparison with Premarin (0.625 mg) alone.

Continued on next page

Prempro—Cont.

3. *Effects during pregnancy.* Use in pregnancy is not recommended.
4. *Gallbladder disease.* Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens. In a large clinical trial, 5 of 1376 subjects taking Premarin alone or Premarin/Cycrin® at doses comparable to PREMPRO or PREMPHASE developed cholecystitis with cholelithiasis that required cholecystectomy.
5. *Elevated blood pressure.* Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. In a large clinical trial, transient elevations from baseline of 40 mm Hg or more systolic and 20 mm Hg or more diastolic were reported in less than 2% and 4% of postmenopausal subjects, respectively. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.
6. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.
7. *Visual abnormalities.* Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

PRECAUTIONS

GENERAL

Based on experience with estrogens and/or progestins:

1. *Cardiovascular risk.* A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy *without added progestins* and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports.

Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri. While the effects of added progestins on the risk of ischemic heart disease are not known, medroxyprogesterone acetate at the doses in PREMPRO or PREMPHASE attenuates much of the favorable effect of conjugated estrogens on HDL levels, although it maintains the favorable effect of conjugated estrogens on LDL levels (see **CLINICAL STUDIES**).

While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiologic evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer risk that has been reported with prolonged estrogen replacement therapy (see **WARNINGS**).

The safety data regarding PREMPRO and PREMPHASE were obtained primarily from clinical trials and epidemiologic studies of postmenopausal Caucasian women, who were at generally low risk for cardiovascular disease and higher than average risk for osteoporosis. The safety profile of PREMPRO and PREMPHASE derived from these study populations cannot necessarily be extrapolated to other populations of diverse racial and/or demographic composition. When considering prescribing PREMPRO or PREMPHASE, physicians are advised to weigh the potential benefits and risks of therapy as applicable to each individual patient.

2. *Use in hysterectomized women.* Existing data do not support the use of the combination of estrogen and progestin in postmenopausal women without a uterus. There are possible risks which may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include some deterioration in glucose tolerance, as reported in a large clinical trial of PREMPRO and PREMPHASE, and less favorable effects on lipid metabolism as compared to the lipid effects of Premarin alone (see **CLINICAL STUDIES**).

Table 3. MEAN PERCENTAGE CHANGE FROM BASELINE LIPID PROFILE VALUES AFTER ONE YEAR OF TREATMENT

	Treatment Groups			
	PREMPRO 0.625 mg/2.5 mg n=90	PREMPRO 0.625 mg/5 mg n=84	PREMPHASE 0.625 mg/5 mg n=95	Premarin 0.625 mg n=86
Lipid Parameter				
Total Cholesterol	-4.7†	-4.2†	-3.5†	0.2
HDL-C	3.5†	3.7†	4.4†	14.1
HDL_2-C	34.7†	40.1†	30.3†	70.8
LDL-C	-10.3	-8.8	-8.7	-7.7
Triglycerides	24.1†	19.1†	27.5†	39.4

†Significantly ($p \leq 0.05$) different from Premarin alone.

3. *Physical examination.* A complete medical and family history should be taken prior to the initiation of any estrogen/progestin therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.
4. *Fluid retention.* Because estrogens/progestins may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
5. *Uterine bleeding.* Certain patients may develop abnormal uterine bleeding. In cases of undiagnosed abnormal uterine bleeding, adequate diagnostic measures are indicated. (See **WARNINGS**.)
6. The pathologist should be advised of estrogen/progestin therapy when relevant specimens are submitted.

Based on experience with estrogens:

1. *Familial hyperlipoproteinemia.* Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.
2. *Hypercoagulability.* Some epidemiological studies have shown that women taking estrogen replacement therapy have hypercoagulability primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have changes in levels of coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low-dose mestranol may increase the risk of thromboembolism in postmenopausal women. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease. In a clinical trial of 1724 patients, in which 204 PREMPRO™-treated patients and 107 PREMPHASE®-treated patients had metabolic studies performed, factors VII and X concentrations and plasminogen activity increased at the end of 1 year, and antithrombin III activity decreased in women receiving PREMPRO 0.625 mg/2.5 mg MPA or PREMPHASE 0.625 mg/5 mg MPA at the end of the year. At the end of the year, antithrombin III activity increased slightly in women receiving PREMPRO 0.625 mg/5.0 mg MPA.
3. *Mastodynia.* Certain patients may develop undesirable manifestations of estrogenic stimulation such as mastodynia. In a large clinical trial of PREMPRO, PREMPHASE, and Premarin®, approximately one third of the subjects receiving PREMPRO and approximately one third of the subjects receiving PREMPHASE reported breast pain during treatment versus 12% for Premarin alone.

Based on experience with progestins:

1. *Lipoprotein metabolism.* See **CLINICAL STUDIES**.
2. *Impaired glucose tolerance.* See *Use in hysterectomized women*, above.
3. *Depression.* Patients who have a history of depression should be observed and the drugs discontinued if the depression recurs to a serious degree.

Information for the Patient

See text of Patient Package Insert which appears after the **HOW SUPPLIED** section.

Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay, T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased glyceride levels.
5. Impaired glucose tolerance. For this reason, diabetic tients should be carefully observed while receiving estro progestin therapy.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.
8. Aminoglutethimide administered concomitantly MPA may significantly depress the bioavailability of M

Carcinogenesis, Mutagenesis, and Impairment of Fertil

Long term continuous administration of natural and s thetic estrogens in certain animal species increases the quency of carcinomas of the breasts, uterus, cervix, vag testis, and liver. (See **CONTRAINDICATIONS**, **WARNINGS**.)

In a two-year oral study of MPA in which female rats w exposed to dosages of up to 5000 µg/kg/day in their diets times higher—based on AUC values—than the level served experimentally in women taking 10 mg of MPA dose-related increase in pancreatic islet cell tumors (enomas and carcinomas) occurred. Pancreatic tumor i dence was increased at 1000 and 5000 µg/kg/day, but no 200 µg/kg/day.

A decreased incidence of spontaneous mammary gland mors was observed in all three MPA-treated groups, co pared to controls, in the two-year rat study. The mechani for the decreased incidence of mammary gland tumors served in the MPA-treated rats may be linked to the sig icant decrease in serum prolactin concentration observed rats.

Beagle dogs treated with MPA developed mammary n ules, some of which were malignant. Although nodules casionally appeared in control animals, they were interm tent in nature, whereas the nodules in the drug-treated a mals were larger, more numerous, persistent, and the were some breast malignancies with metastases. It known that progestogens stimulate synthesis and release growth hormone in dogs. The growth hormone, along wi the progestogen, stimulates mammary growth and tumo In contrast, growth hormone in humans is not increas nor does growth hormone have any significant ma motrophic role. Therefore, the MPA-induced increase mammary tumors in dogs probably has no significance humans. No pancreatic tumors occurred in dogs.

Pregnancy Category X

Estrogens/progestins should not be used during pregnan See **CONTRAINDICATIONS**.

Nursing Mothers

As a general principle, the administration of any drug nursing mothers should be done only when clearly nec sary since many drugs are excreted in human milk. Est gen administration to nursing mothers has been shown decrease the quantity and quality of the milk. Detectat amounts of progestin have been identified in the milk mothers receiving the drug. The effect of this on the nursi infant has not been determined.

ADVERSE REACTIONS

(See **WARNINGS** regarding induction of neoplasia, adver effects on the fetus, increased incidence of gallbladder di ease, elevated blood pressure, thromboembolic disorders, sual abnormalities, and hypercalcemia and **PRECAU TIONS** for cardiovascular disease.)

In a one year clinical trial that included 678 women treate with PREMPRO, 351 women treated with PREMPHASI and 347 women treated with Premarin, the following a verse events occurred at a rate ≥ 5% (see Table 4):

[See table 4 at top of next page]

The following adverse reactions also have been reporte with estrogen and/or progestin therapy:

Genitourinary system. Changes in vaginal bleeding patter and abnormal withdrawal bleeding or flow, breakthroug bleeding, spotting, change in amount of cervical secretio premenstrual-like syndrome, cystitis-like syndrome, i crease in size of uterine leiomyomata, vaginal candidiasi amenorrhea, changes in cervical erosion.

Breasts. Tenderness, enlargement, galactorrhea.

Gastrointestinal. Nausea, cholestatic jaundice, changes i appetite, vomiting, abdominal cramps, bloating, increase incidence of gallbladder disease, pancreatitis.

Skin. Chloasma or melasma that may persist when drug i discontinued, erythema multiforme, erythema nodosum hemorrhagic eruption, loss of scalp hair, hirsutism, itching urticaria, pruritus, generalized rash, rash (allergic) wit and without pruritus, acne.

Cardiovascular. In susceptible individuals, change in bloo pressure, thrombophlebitis, pulmonary embolism, cerebra thrombosis and embolism.

.S. Headache, dizziness, mental depression, nervousness, raine, chorea, insomnia, somnolence.
s. Neuro-ocular lesions, e.g., retinal thrombosis and optneuritis. Steepening of corneal curvature, intolerance of tact lenses.
cellaneous. Increase or decrease in weight, edema, nges in libido, fatigue, backache, reduced carbohydrate rance, aggravation of porphyria, pyrexia, anaphylactoid tions, anaphylaxis.

JTE OVERDOSAGE

ous ill effects have not been reported following acute inion of large doses of estrogen/progestin-containing oral raceptives by young children. Overdosage may cause sea and vomiting, and withdrawal bleeding may occur males.

SAGE AND ADMINISTRATION

MPRO therapy consists of a single tablet to be taken daily.
or treatment of moderate-to-severe vasomotor symptoms and vulval and vaginal atrophy associated with enopause, patients should be started at the lowest effective dose—PREMPRO 0.625 mg/2.5 mg daily. Patients ould be reevaluated at 3-month to 6-month intervals to termine if treatment for symptoms is still necessary. dequate diagnostic measures, including endometrial mpling when indicated, should be undertaken to rule t malignancy in cases of undiagnosed persistent or rerring abnormal vaginal bleeding. In patients where eeding or spotting remains a problem, after appropriate aluation, consideration should be given to increasing e MPA dose to PREMPRO 0.625 mg/5 mg daily. This se can be periodically reassessed by the health care ovider.
r prevention of osteoporosis—PREMPRO 0.625 mg/2.5 g daily. Patients should be monitored closely for signs of dometrial cancer, and appropriate diagnostic measures ould be taken to rule out malignancy in the event of rsistent or recurring abnormal vaginal bleeding. In paents where bleeding or spotting remains a problem, afappropriate evaluation, consideration should be given increasing the MPA dose to PREMPRO 0.625 mg/5 mg ly. This dose can be periodically reassessed by the ulth care provider.
PHASE therapy consists of two separate tablets; one n 0.625 mg Premarin tablet taken daily on days 1 gh 14 and one light-blue tablet, containing 0.625 mg gated estrogens and 5 mg of medroxyprogesterone actaken on days 15 through 28.
treatment of moderate to severe vasomotor symptis and vulvar and vaginal atrophy associated with opause. Patients should be reevaluated at 3-month to onth intervals to determine if treatment for symps is still necessary. Adequate diagnostic measures, inling endometrial sampling when indicated, should be ertaken to rule out malignancy in cases of undiagd persistent or recurring abnormal vaginal bleeding. prevention of osteoporosis. Treated patients with an ct uterus should be monitored closely for signs of enetrial cancer, and appropriate diagnostic measures uld be taken to rule out malignancy in the event of istent or recurring abnormal vaginal bleeding.

SUPPLIED

PRO™ therapy consists of a single tablet to be taken ily.
PRO 0.625 mg/2.5 mg
rton includes 3 EZ DIAL™ dispensers containing 28
One EZ DIAL™ dispenser contains 28 oval, peach containing 0.625 mg of the conjugated estrogens n Premarin® tablets and 2.5 mg of medroxyprogesacetate for oral administration.
'RO 0.625 mg/5 mg
rton includes 3 EZ DIAL™ dispensers containing 28
One EZ DIAL™ dispenser contains 28 oval, lightolets containing 0.625 mg of the conjugated estrond in Premarin® tablets and 5 mg of medroxyproe acetate for oral administration.
HASE® therapy consists of two separate tablets; oon Premarin® tablet taken daily on days 1 through ne light-blue tablet taken on days 15 through 28.
ton includes 3 EZ DIAL™ dispensers containing 28
One EZ DIAL™ dispenser contains 14 oval, maroon n tablets containing 0.625 mg of conjugated estrol 14 oval, light-blue tablets that contain 0.625 mg of ugated estrogens found in Premarin tablets and 5 droxyprogesterone acetate (MPA) for oral adminis-

earance of PREMPRO™ tablets is a trademark of yerst Laboratories.
arance of Premarin® tablets is a trademark of Wyst Laboratories. The appearance of the conjugated /medroxyprogesterone acetate combination tablets tered trademark.
controlled room temperature 20°C–25°C (68°F–

IATION FOR THE PATIENT

ician has prescribed PREMPRO or PREMPHASE, ation of two hormones, an estrogen and a progesleaflet describes the major benefits and risks of tment, as well as how and when treatment should

O and PREMPHASE replace the hormones in which naturally decrease at menopause. The hormone combination you will be taking has been shown to provide the benefits of estrogen replacement therapy while lowering the frequency of a possible precancerous condition of the uterine lining. This therapy is not intended for women who have had a hysterectomy (surgical removal of the uterus).

Estrogens have several important uses but also some risks. You must decide, with your doctor, whether the risks of estrogens are acceptable when weighed against their benefits. The length of treatment with estrogens can vary from woman to woman. Check with your doctor to make sure you are using the lowest possible effective dose.

With PREMPRO or PREMPHASE therapy several menstrual-like bleeding patterns may occur. These may range from absence of bleeding to irregular bleeding. If bleeding occurs, it is frequently light spotting or moderate menstrual-like bleeding, but it may be heavy. If you experience vaginal bleeding while taking PREMPRO or PREMPHASE, you should discuss your bleeding pattern with your doctor and set up an appropriate schedule for follow-up care.

Table 4. ALL TREATMENT EMERGENT STUDY EVENTS REGARDLESS OF DRUG RELATIONSHIP REPORTED AT A FREQUENCY ≥ 5%

	Regimen A PREMPRO 0.625 mg/2.5 mg continuous (n=340)	Regimen B PREMPRO 0.625 mg/5.0 mg continuous (n=338)	Regimen C PREMPHASE 0.625 mg/5.0 mg cyclic sequential (n=351)	Regimen E PREMARIN 0.625 mg (n=347)
Body as a whole				
abdominal pain	16%	21%	23%	17%
accidental injury	5%	4%	5%	5%
asthenia	6%	8%	10%	8%
back pain	14%	13%	16%	14%
flu syndrome	10%	13%	12%	14%
headache	36%	28%	37%	38%
infection	16%	16%	18%	14%
pain	11%	13%	12%	13%
pelvic pain	4%	5%	5%	5%
Digestive system				
diarrhea	6%	6%	5%	10%
dyspepsia	6%	6%	5%	5%
flatulence	8%	9%	8%	5%
nausea	11%	9%	11%	11%
Metabolic and Nutritional				
peripheral edema	4%	4%	3%	5%
Musculoskeletal system				
arthralgia	9%	7%	9%	7%
leg cramps	3%	4%	5%	4%
Nervous system				
depression	6%	11%	11%	10%
dizziness	5%	3%	4%	6%
hypertonia	4%	3%	3%	7%
Respiratory system				
pharyngitis	11%	11%	13%	12%
rhinitis	8%	6%	8%	7%
sinusitis	8%	7%	7%	5%
Skin and appendages				
pruritus	10%	8%	5%	4%
rash	4%	6%	4%	3%
Urogenital system				
breast pain	33%	38%	32%	12%
cervix disorder	4%	4%	5%	5%
dysmenorrhea	8%	5%	13%	5%
leukorrhea	6%	5%	9%	8%
vaginal hemorrhage	2%	1%	3%	6%
vaginitis	7%	7%	5%	3%

USES OF ESTROGEN

To reduce moderate to severe menopausal symptoms. Estrogens are hormones produced by the ovaries of normal women. When a woman is between the ages of 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels that causes the "change of life" or menopause (the end of monthly menstrual periods). A sudden drop in estrogen levels also occurs if both ovaries are removed during an operation before natural menopause takes place. This is referred to as "surgical menopause." When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. In some women the symptoms are mild; in others they can be severe. These symptoms may last only a few months or longer. Taking PREMPRO or PREMPHASE can alleviate these symptoms. If you are not taking hormones for other reasons, such as the prevention of osteoporosis, you should take PREMPRO or PREMPHASE only as long as you need it for relief from your menopausal symptoms.

To prevent thinning of bones. Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists, and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either from diet (such as dairy products) or from calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.

Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics:

- White or Asian race
- Small, slim body frame
- Cigarette-smoking habit
- Family history of osteoporosis (in a mother, sister, or aunt)
- Early menopause either natural or because of surgical removal of ovaries ("surgical menopause")

To treat vulvar and vaginal atrophy (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.

WHO SHOULD NOT USE ESTROGENS

During pregnancy. If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.

If you have unusual vaginal bleeding which has not been evaluated by your doctor. Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

If you have had cancer. Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus.

If you have any circulation problems. Estrogen drugs should not be used except in unusually special situations in which your doctor decides that you need estrogen therapy so

Continued on next page

Prempro—Cont.

much that the risks are acceptable. Women with abnormal blood clotting conditions should avoid estrogen use (see **RISKS OF ESTROGENS AND/OR PROGESTINS**).

When they do not work. During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

After childbirth or when breastfeeding a baby. Estrogen should not be used to try to stop the breast from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see **RISKS OF ESTROGENS AND/OR PROGESTINS**).

If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health-care provider.

RISKS OF ESTROGENS AND/OR PROGESTINS

Cancer of the uterus. If you use any drug which contains estrogen, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

The risk of cancer of the uterus increases when estrogens are used alone, the longer they are used, and when larger doses are taken. There is a higher risk of cancer of the uterus if you are overweight, diabetic, or have high blood pressure. The hormone combination you will be taking contains estrogen and progestin. This combination has been shown to provide the benefits of estrogen replacement therapy for the **USES OF ESTROGEN** listed above, while reducing the risk of a precancerous condition of the uterine lining (see **OTHER INFORMATION,** below).

However, additional risks may be associated with the inclusion of a progestin in estrogen treatment. The possible risks include less favorable effects on blood fats as compared to Premarin alone, unfavorable effects on blood sugars, and a possible increase in breast cancer risk (see *Cancer of the breast,* below). Usually, the smaller the dose and the shorter the duration of treatment, the more these effects are minimized. Check with your doctor to make sure you are using the lowest effective dose and only for as long as you need it.

If you have had your uterus removed, there is no risk of developing cancer of the uterus and no benefit to be gained by using a combination estrogen/progestin product.

Cancer of the breast. Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used high doses for shorter time periods. The effects of added progestin on the risk of breast cancer are unknown. Some studies have reported a somewhat increased risk, even higher than the possible risk associated with estrogens alone. Others have not. Regular breast examinations by a health professional and monthly self-examination are recommended for all women. Regular mammograms are recommended for all women over 50 years of age.

Gallbladder disease. Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

Inflammation of the Pancreas. Women with high triglyceride levels may have an increased risk of developing inflammation of the pancreas.

Abnormal blood clotting. Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long-term disability.

Excess calcium in the blood. Taking estrogens may lead to severe hypercalcemia in women with breast and/or bone cancer.

During pregnancy. There is an increased risk of birth defects in children whose mothers take this drug during the first four months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies. The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5 to 8 per 1,000 male births and is about doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses. However, enlargement of the clitoris and fusion of the labia may occur, although rarely.

Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy. These drugs have been used as a test for pregnancy, but this is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available. If you take PREMPRO or PREMPHASE and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

SIDE EFFECTS WITH ESTROGENS AND/OR PROGESTINS

In addition to the risks listed above, the following side effects have been reported with estrogen and/or progestin use:

- Nausea, vomiting, pain, cramps, swelling, or tenderness in the abdomen.
- Yellowing of the skin and/or whites of the eyes.
- Breast tenderness or enlargement.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Irregular bleeding or spotting.
- Change in amount of cervical secretion.
- Vaginal yeast infections.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face; reddening of the skin; skin rashes.
- Worsening of porphyria.
- Headache, migraines, dizziness, faintness, or changes in vision (including intolerance to contact lenses).
- Mental depression.
- Involuntary muscle spasms.
- Hair loss or abnormal hairiness.
- Increase or decrease in weight.
- Changes in sex drive.
- Possible changes in blood sugar.

REDUCING THE RISKS OF ESTROGEN/PROGESTIN

If you decide to take an estrogen/progestin combination, you can reduce your risks by carefully monitoring your treatment.

See your doctor regularly. While you are taking PREMPRO or PREMPHASE, it is important to visit your doctor at least once a year for a checkup. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast X ray), you may need to have more frequent breast examinations.

Reassess your need for treatment. You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble. If any of these warning signals (or any other unusual symptoms) happen while you are using estrogen/progestin, call your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine abnormality).
- Pains in the calves or chest, a sudden shortness of breath or coughing blood (indicating possible clots in the legs, heart, or lungs).
- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (indicating possible clots in the brain or eye).
- Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly).
- Yellowing of the skin and/or whites of the eyes (possible liver problems).
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormonal drug, with estrogens lowers the risk of developing this condition. Therefore, since your uterus has not been removed, your doctor has prescribed PREMPRO or PREMPHASE, which includes both a progestin and estrogens.

You should know, however, that taking estrogens *with* progestins may have unhealthy effects on blood sugar, which might make a diabetic condition worse. Additional risks include a possible further increase in breast cancer risk which may be associated with long-term estrogen use. Some research has shown that estrogens taken *without* progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health-care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about the amounts recommended.

4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital, or poison control center immediately.

5. This leaflet provides the most important information about PREMPRO and PREMPHASE. If you want to read more, ask your doctor or pharmacist to let you read the professional labeling. The professional labeling is also published in a book called *The Physicians' Desk Reference* which is available in bookstores and public libraries.

HOW SUPPLIED

PREMPRO™ is a combination of the conjugated estrogens found in Premarin® tablets and medroxyprogesterone acetate (MPA). Depending on the dosage strength, PREMPRO therapy consists of either a single peach tablet or a single light-blue tablet to be taken once daily.

PREMPRO 0.625 mg/2.5 mg

Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL™ dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin® tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

PREMPRO 0.625 mg/5 mg

Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL™ dispenser contains 28 oval, light blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin® tablets and 5 mg of medroxyprogesterone acetate for oral administration.

The appearance of PREMPRO™ tablets is a trademark of Wyeth-Ayerst Laboratories.

PREMPHASE® is a combination of two separate tablets one maroon Premarin® tablet taken daily on days 1 through 14 and one light-blue tablet taken on days 15 through 28. Each carton includes 3 EZ DIAL™ dispensers containing 28 tablets. One EZ DIAL™ dispenser contains 14 oval, maroon Premarin tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate (MPA) for oral administration.

The appearance of Premarin® tablets is a trademark of Wyeth-Ayerst Laboratories. The appearance of the conjugated estrogens/medroxyprogesterone acetate combination tablets is a registered trademark.

Keep out of reach of children.

Store at controlled room temperature 20° C–25° C (68° F–77° F).

Manufactured by:
Ayerst Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

Shown in Product Identification Guide, page 343

PROTOPAM® CHLORIDE

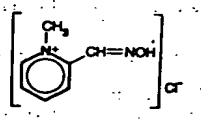
(pralidoxime chloride)
Lyophilized Powder for Injection

Caution: Federal law prohibits dispensing without prescription.

DESCRIPTION

Chemical name: 2-formyl-1-methylpyridinium chloride oxime. Available in the United States as Protopam Chloride, pralidoxime chloride is frequently referred to as 2-PAM Chloride.

Structural formula:



Pralidoxime chloride occurs as an odorless, white, nonhygroscopic, crystalline powder which is soluble in water to the extent of 1 g in less than 1 mL. Stable in air, it melts between 215° and 225°C, with decomposition.

The specific activity of the drug resides in the 2-formyl-1-methylpyridinium ion and is independent of the particular salt employed. The chloride is preferred because of physiologic compatibility, excellent water solubility at all temperatures, and high potency per gram, due to its low (173) molecular weight.

Pralidoxime chloride is a cholinesterase reactivator.

Protopam Chloride for intravenous injection or infusion is prepared by cryodesiccation. Each vial contains 1 g of sterile pralidoxime chloride, and NaOH to adjust pH, to be reconstituted with 20 mL of Sterile Water for Injection, USP. The pH of the reconstituted solution is 3.5 to 4.5. Intramuscular or subcutaneous injection may be used when intravenous injection is not feasible.

CLINICAL PHARMACOLOGY

The principal action of pralidoxime is to reactivate cholinesterase (mainly outside of the central nervous system which has been inactivated by phosphorylation due to an organophosphate pesticide or related compound. The destruction of accumulated acetylcholine can then proceed and neuromuscular junctions will again function normally. Pralidoxime also slows the process of "aging" of phosphorylated cholinesterase to a nonreactivatable form, and definitely fies certain organophosphates by direct chemical reaction. The drug has its most critical effect in relieving paralysis of the muscles of respiration. Because pralidoxime is less effective in relieving depression of the respiratory center, atropine is always required concomitantly to block the effect of accumulated acetylcholine at this site. Pralidoxime relieves muscarinic signs and symptoms, salivation, bronchospasm, etc., but this action is relatively unimportant since atropine is adequate for this purpose.